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(54) Prolineamide derivatives.

(57) A prolineamide derivative represented by the formula (I):

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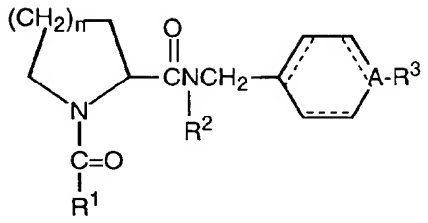


(I)

or a salt or hydrate thereof or a pharmaceutically acceptable salt thereof, which has a protease inhibition activity and is usuful as an active ingredient of pharmaceutical compositions is provided.

FIELD OF THE INVENTION

The present invention relates to novel proline derivatives. More particularly, it relates to proline derivatives having a protease inhibition activity or pharmaceutically acceptable salts thereof and protease inhibitors containing the same as an active ingredient.

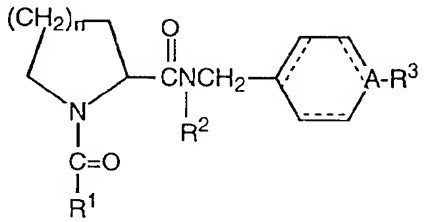
BACKGROUND OF THE INVENTION

It has been known that various proteases are present in the living body, for example, a group of serine proteases such as thrombin, factor Xa, factor IXa, factor VIIa, trypsin, plasmin, tissue plasminogen activator, kallikrein, C3/C5 convertase in the complement system, tryptase, etc. is known. Further, it is also known that these proteases cause various diseases when they are activated abnormally by some reason. Accordingly, substances which inhibit the activity of these proteases are useful as a clinical remedy. For example, antithrombin agents, anti-factor Xa agents and anti-factor VIIa agents are useful for treating thrombosis, antitrypsin agents are useful for treating pancreatitis, antiplasmin agents are useful as hemostatics, antiallergic agents and antiinflammatory agents, antikallikrein agents are useful as a remedy for inflammation and ulcer, and anticomplementary agents are useful as a remedy for nephritis and rheumatoid arthritis. Protease inhibitors having these actions have hitherto been developed, but they are not necessarily sufficient for practical use in view of protease inhibition activity, stability in the living body and the like. For example, tripeptide derivatives consist of arginine derivatives are known as protease inhibitors. That is, D-phenylalanyl-L-prolyl-L-arginal is known as a thrombin inhibitor (e.g. Folia Haematol., 109, 22 (1982)) but is fairly unstable in the living body (J. Med. Chem., 33, 1729 (1990)). Further, arginal derivatives (Japanese Laid-open Patent Publication No. 4-89498) or amidinophenylalanine derivatives (Thromb. Res., 17, 425 (1980)) are reported as protease inhibitors but their inhibition activity is low.

Under these circumstances, the present inventors have studied to develop structurally novel drugs having enzyme inhibition activity and stability in vivo, which are sufficient for practical use. As a result, it has been found that certain prolineamide derivatives can attain the desired object, thus the present invention has been established.

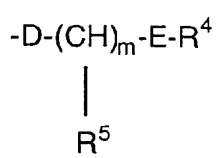
SUMMARY OF THE INVENTION

That is, the present invention provides a prolineamide derivative represented by the formula (I):



(I)

wherein A is a carbon atom or a nitrogen atom; n is an integer of 0 to 2; a broken line is absent or a single bond;
R^1 is



{wherein D and E independently indicate a single bond or an optionally branched C_1-C_6 alkylene group;
R^4 is a C_1-C_6 alkyl group, -OR^6 (R^6 is a hydrogen atom, a C_1-C_6 alkyl group, an optionally substituted

C_6-C_{10} aryl group, an optionally substituted C_3-C_8 cycloalkyl group or an optionally substituted C_7-C_{12} aralkyl group), -SR^7 (R^7 is a C_1-C_6 alkyl group, an optionally substituted C_6-C_{10} aryl group, an optionally substituted C_3-C_8 cycloalkyl group or an optionally substituted C_7-C_{12} aralkyl group), -SOR^8 (R^8 is an optionally substituted C_6-C_{10} aryl group or an optionally substituted C_3-C_8 cycloalkyl group), -SO_2R^9 (R^9 is an optionally substituted C_6-C_{10} aryl group or an optionally substituted C_3-C_8 cycloalkyl group), -COR^{10} - (R^{10} is a hydroxyl group, a C_1-C_6 alkoxy group, an optionally substituted C_6-C_{10} aryl group or an optionally substituted C_3-C_8 cycloalkyl group), -NHR^{11} (R^{11} is a C_1-C_6 alkyl group, an optionally substituted C_6-C_{10} aryl group, an optionally substituted C_3-C_8 cycloalkyl group or an optionally substituted C_7-C_{12} aralkyl group), -$NHCOR^{12}$ (R^{12} is a C_1-C_6 alkoxy group, an optionally substituted C_6-C_{10} aryl group, an optionally substituted C_3-C_8 cycloalkyl group or an optionally substituted C_7-C_{12} aralkyloxy group), -$NHSO_2R^{13}$ (R^{13} is a C_1-C_6 alkyl group, an optionally substituted C_6-C_{10} aryl group, an optionally substituted C_3-C_8 cycloalkyl group, an optionally substituted C_7-C_{12} aralkyl group, an optionally substituted 5- to 10-membered heterocyclic group), an optionally substituted C_6-C_{10} aryl group, an optionally substituted C_3-C_8 cycloalkyl group, an optionally substituted 5- to 10-membered heterocyclic group or -$SiR^{14}R^{15}R^{16}$ (R^{14}, R^{15}, and R^{16} independently indicate a C_1-C_6 alkyl group);

R^5 is a -OR^{17} (R^{17} is a hydrogen atom, -$SiR^{22}R^{23}R^{24}$ (R^{22}, R^{23}, and R^{24} independently indicate a C_1-C_6 alkyl group), a C_1-C_6 alkyl group or an optionally substituted 5- to 10-membered heterocyclic group)), -$OCOR^{18}$ (R^{18} is a hydrogen atom, a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, an amino group, a C_1-C_6 alkylamino group, a C_2-C_{12} dialkylamino group or a C_2-C_7 alkenylamino group), -NHR^{19} (R^{19} is a hydrogen atom, a C_1-C_6 alkyl group or an optionally substituted C_7-C_{12} aralkyl group), -$NHCOR^{20}$ (R^{20} is a hydrogen atom, a C_1-C_6 alkyl group, a C_1-C_6 haloalkyl group, a C_1-C_6 alkoxy group, an optionally substituted C_3-C_8 cycloalkyl group, a C_2-C_7 carboxyalkyloxy group, a C_2-C_7 alkenyloxy group, an optionally substituted C_6-C_{10} aryl group, an optionally substituted C_6-C_{10} aryloxy group, a C_3-C_9 alkoxycarbonylalkoxy group, a C_2-C_{12} dialkylamino group or an optionally substituted C_7-C_{12} aralkyloxy group) or -$NHSO_2R^{21}$ (R^{21} is a C_1-C_6 alkyl group, a C_1-C_6 haloalkyl group, a C_2-C_7 carboxyalkyl group, an optionally substituted C_6-C_{10} aryl group, a C_3-C_9 alkoxycarbonylalkyl group or an optionally substituted C_7-C_{12} aralkyl group); and m is 0 or 1};

R^2 is a hydrogen atom or a C_1-C_6 alkyl group; and R^3 is -$C(=NR^{25})NH_2$ (R^{25} is a hydrogen atom, a C_1-C_6 alkyl group, a C_2-C_7 acyl group, a C_2-C_7 acyloxy group, a C_1-C_6 alkoxy group, a C_2-C_7 alkoxycarbonyl group, a C_2-C_7 alkoxycarbonyloxy group, a hydroxyl group or a C_2-C_7-hydroxyalkylcarbonyloxy group), -NH-$C(=NR^{25})NH_2$ (R^{25} is as defined above) or -NHR^{26} (R^{26} is a hydrogen atom, a C_1-C_6 alkyl group, a C_2-C_7 acyl group, a C_2-C_7 alkoxycarbonyl group or a 5-C_1-C_3 alkyl-1,3-dioxol-2-on-4-ylmethyl group; provided that R^3 is -$C(=NR^{25})NH_2$ when A is a nitrogen atom or a salt and pharmaceutical use thereof.

DETAILED DESCRIPTION OF THE INVENTION

The prolineamide derivative of the present invention is represented by the above formula (I). Examples of the optionally branched C_1-C_6 alkylene group in the above definition include -CH_2-, -$(CH_2)_2$-, -$(CH_2)_3$-, -$(CH_2)_4$-,-$(CH_2)_5$-, -$(CH_2)_6$-, -$CH(CH_3)$-, -$C(CH_3)_2$-, -$CH(CH_3)CH_2$-, -$CH_2CH(CH_3)$-, -$C(CH_3)_2CH_2$-, -$CH_2C(CH_3)_2$-, -$CH(CH_3)CH(CH_3)$- and the like. Examples of the C_1-C_6 alkyl group include methyl group, ethyl group, n-propyl group, i-propyl group, n-butyl group, s-butyl group, i-butyl group, t-butyl group, n-pentyl group, n-hexyl group and the like. Examples of the C_1-C_3 alkyl group include those having three carbon atoms or less among those illustrated above. Examples of the C_1-C_6 alkoxy group include methoxy group, ethoxy group, n-propoxy group, i-propoxy group, n-butyloxy group, s-butyloxy group, i-butyloxy group, t-butyloxy group, n-pentyloxy group, n-hexyloxy group and the like. Examples of the C_2-C_7 alkoxycarbonyl group include methoxycarbonyl group, ethoxycarbonyl group, n-propoxycarbonyl group, i-propoxycarbonyl group, n-butyloxycarbonyl group, t-butyloxycarbonyl group, n-pentyloxycarbonyl group, n-hexyloxycarbonyl group and the like. Examples of the C_3-C_8 cycloalkyl group include cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group, cyclooctyl group and the like. Examples of the C_6-C_{10} aryl group include phenyl group, tolyl group, naphthyl group and the like. Examples of the C_7-C_{12} aralkyl group include benzyl group, phenylethyl group, phenylpropyl group, naphthylmethyl group and the like. Examples of the C_6-C_{10} aryloxy group include phenyloxy group, naphthyloxy group and the like. Examples of the C_7-C_{12} aralkyloxy group include benzyloxy group, phenylethyloxy group, phenylpropyloxy group, naphthylmethyloxy group and the like. Examples of the heterocyclic group include those contain 1 to 4 heteroatoms selected from an oxygen atom, a sulfur atom and a nitrogen atom and the total number of atoms constituting the ring is 5 to 10, specifically, respective residues of furan ring, tetrahydrofuran ring, pyran ring, benzofuran ring, chroman ring, thiophene ring, benzothiophene ring, pyrrole ring, imidazole ring, pyrazole ring, triazole ring, pyridine ring, piperidine ring, pyrazine ring, piperazine ring, pyrimidine ring,

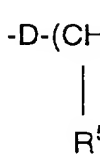
indole ring, benzimidazole ring, purine ring, quinoline ring, phthalazine ring, quinazoline ring, cinnoline ring, oxazole ring, thiazole ring, morpholine ring and the like. Examples of the C_1-C_6 haloalkyl group include chloromethyl group, bromomethyl group, dichloromethyl group, 1-chloroethyl group, 2-chloroethyl group, 3-chloropropyl group, 4-chlorobutyl group, 5-chloropentyl group, 6-chlorohexyl group, difluoromethyl group, trifluoromethyl group and the like. Examples of the C_2-C_7 carboxyalkyl group include carboxymethyl group, 2-carboxyethyl group, 3-carboxypropyl group, 4-carboxybutyl group, 5-carboxypentyl group, 6-carboxyhexyl group and the like. Examples of the C_2-C_7 carboxyalkyloxy group include carboxymethoxy group, 2-carboxyethoxy group, 3-carboxypropoxy group, 4-carboxybutyloxy group, 5-carboxypentyloxy group, 6-carboxyhexyloxy group and the like. Examples of the C_2-C_7 alkenyloxy group include vinyloxy group, aryloxy group, 2-propenyloxy group, isopropenyloxy group, 3-butenyloxy group, 4-pentenyloxy group, 5-hexenyloxy group and the like. Examples of the C_2-C_7 alkenylamino group include vinylamino group, arylamino group, 2-propenylamino group, isopropenylamino group, 3-butenylamino group, 4-pentenylamino group, 5-hexenylamino group and the like. Examples of the C_1-C_6 alkylamino group include methylamino group, ethylamino group, n-propylamino group, n-butylamino group and the like. Examples of the C_2-C_{12} dialkylamino group include dimethylamino group, methylethylamino group, diethylamino group, di-n-propylamino group and the like. Examples of the C_2-C_7 acyl group include acetyl group, propionyl group, butyryl group, isobutyryl group, valeryl group, isovaleryl group, pivaroyl group, hexanoyl group, heptanoyl group and the like. Examples of the C_2-C_7 acyloxy group include acetyloxy group, propionyloxy group, butyryloxy group, isobutyryloxy group, valeryloxy group, isovaleryloxy group, pivaroyloxy group, hexanoyloxy group, heptanoyloxy group and the like. Examples of the C_2-C_7 alkokycarbonyloxy group include methoxycarbonyloxy group, ethoxycarbonyloxy group, n-propoxycarbonyloxy group, n-butyloxycarbonyloxy group, n-pentyloxycarbonyloxy group, n-hexyloxycarbonyloxy group and the like. Examples of the C_2-C_7 hydroxyalkylcarbonyloxy group include hydroxymethylcarbonyloxy group, 2-hydroxyethylcarbonyloxy group, 3-hydroxypropylcarbonyloxy group, 4-hydroxybutylcarbonyloxy group, 5-hydroxypentylcarbonyloxy group, 6-hydroxyhexylcarbonyloxy group and the like. Examples of the C_3-C_9 alkoxycarbonylalkoxy group include methoxycarbonylmethoxy group, ethoxycarbonylmethoxy group, propoxycarbonylmethoxy group, methoxycarbonylethoxy group, ethoxycarbonylethoxy group, propoxycarbonylethoxy group and the like. Examples of the C_3-C_9 alkoxycarbonylalkyl group include methoxycarbonylmethyl group, ethoxycarbonylmethyl group, propoxycarbonylmethyl group, methoxycarbonylethyl group, methoxycarbonylmethyl group, propoxycarbonylethyl group and the like.

Examples of the substituent in the above definition of "optionally substituted (with substituent)" include above-described C_1-C_6 alkyl group; above-described C_1-C_6 haloalkyl group; above-described C_1-C_6 alkoxy group; hydroxyl group; carboxyl group; above-described C_2-C_7 carboxyalkyl group; above-described C_2-C_7 carboxyalkyloxy group; above-described C_2-C_7 acyl group; above-described C_2-C_7 acyloxy group; above-described C_2-C_7 alkoxycarbonyl group; above-described C_2-C_7 alkoxycarbonyloxy group; C_8-C_{13} aralkyloxycarbonyl group such as benzyloxycarbonyl group, phenylethyloxycarbonyl group, phenylpropyloxycarbonyl group, naphthylmethyloxycarbonyl group, etc.; halogen atoms such as fluorine atom, chlorine atom, bromine atom and the like.

In the compound represented by the above formula (I), it is preferred that the 5- to 6-membered contains 1 to 4 heteroatoms selected from the group consisting of an oxygen atom, a sulfur atom and a nitrogen atom and the total number of atoms constituting the ring is 5 to 10. Further, as the substituent of the respective groups, a group(s) selected from C_1-C_6 alkyl group, C_1-C_6 haloalkyl group, C_1-C_6 alkoxy group, hydroxyl group, carboxyl group, C_2-C_7 carboxyalkyl group, C_2-C_7 carboxyalkyloxy group, C_2-C_7 acyl group, C_2-C_7 acyloxy group, C_2-C_7 alkoxycarbonyl group, C_2-C_7 alkoxycarbonyloxy group, C_8-C_{13} aralkyloxycarbonyl group, C_3-C_9 alkoxycarbonylalkoxy group and halogen atoms is preferred.

In the compound represented by the above formula (I) of the present invention, a carbon atom is preferred as A.

Examples of preferred compounds of the present invention include those of the formula (I), wherein A is a carbon atom; n is 1 or 2; R^1 is



(wherein D and E independently indicate a single bond or an optionally branched C_1-C_6 alkylene group;

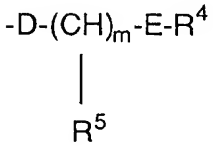
R^4 is a C_1-C_6 alkyl group: -OR^6 (R^6 is a C_1-C_6 alkyl group; a C_6-C_{10} aryl group which may be substituted with at least one substituent selected from the group consisting of a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a halogen atom, a hydroxyl group, a carboxyl group, a C_2-C_7 alkoxycarbonyl group, a C_2-C_7 carboxyalkyl group, a C_2-C_7 acyl group, a C_2-C_7 acyloxy group, a C_2-C_7 alkoxycarbonyloxy group, a C_3-C_9 alkoxycarbonylalkoxy group and a benzyloxycarbonyl group; or a C_7-C_{12} aralkyl group which may be substituted with at least one substituent selected from the group consisting of a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a halogen atom, a hydroxyl group, a carboxyl group, a C_2-C_7 alkoxycarbonyl group, a C_2-C_7 carboxyalkyl group, a C_2-C_7 acyl group, a C_2-C_7 acyloxy group, a C_2-C_7 alkoxycarbonyloxy group, a C_3-C_9 alkoxycarbonylalkoxy group and a benzyloxycarbonyl group): -SR^7 (R^7 is a C_1-C_6 alkyl group, a C_6-C_{10} aryl group which may be substituted with at least one substituent selected from the group consisting of a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a halogen atom, a hydroxyl group, a carboxyl group, a C_2-C_7 alkoxycarbonyl group, a C_2-C_7 carboxyalkyl group, a C_2-C_7 acyl group, a C_2-C_7acyloxy group, a C_2-C_7 alkoxycarbonyloxy group, a C_3-C_9 alkoxycarbonylalkoxy group and a benzyloxycarbonyl group; or a C_7-C_{12} aralkyl group which may be substituted with at least one substituent selected from the group consisting of a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a halogen atom, a hydroxyl group, a carboxyl group, a C_2-C_7 alkoxycarbonyl group, a C_2-C_7 carboxyalkyl group, a C_2-C_7 acyl group, a C_2-C_7 acyloxy group, a C_2-C_7 alkoxycarbonyloxy group, a C_3-C_9 alkoxycarbonylalkoxy group and a benzyloxycarbonyl group): -COOH: a C_6-C_{10} aryl group which may be substituted with at least one substituent selected from the group consisting of a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a halogen atom, a hydroxyl group, a carboxyl group, a C_2-C_7 alkoxycarbonyl group, a C_2-C_7 carboxyalkyl group, a C_2-C_7 acyl group, a C_2-C_7 acyloxy group, a C_2-C_7 alkoxycarbonyloxy group, a C_3-C_9 alkoxycarbonylalkoxy group and a benzyloxycarbonyl group: a C_3-C_8 cycloalkyl group: or -$SiR^{14}R^{15}R^{16}$ (R^{14}, R^{15}, and R^{16} independently indicate a C_1-C_6 alkyl group);

R^5 is -OH, -$OCOR^{18}$ (R^{18} is a C_1-C_6 alkoxy group or a C_2-C_7 alkenylamino group), -NH_2, -$NHCOR^{20}$ -(R^{20} is a C_1-C_6 alkoxy group, a C_6-C_{10} aryloxy group, a C_3-C_9 alkoxycarbonylalkoxy group, a C_2-C_{12} dialkylamino group or a C_7-C_{12} aralkyloxy group) or -$NHSO_2R^{21}$ (R^{21} is a C_1-C_6 alkyl group, a C_2-C_7 carboxyalkyl group, a C_6-C_{10} aryl group, a C_3-C_9 alkoxycarbonylalkyl group or a C_7-C_{12} aralkyl group); and m is 0 or 1};

R^2 is a hydrogen atom; and

R^3 is -$C(=NR^{25})NH_2$ (R^{25} is a hydrogen atom, a C_2-C_7 alkoxycarbonyl group or a hydroxyl group), -NH-$C(=NR^{25})NH_2$ (R^{25} is as defined above) or -NHR^{26} (R^{26} is a hydrogen atom, a C_2-C_7 alkoxycarbonyl group or a 5-C_1-C_3 alkyl-1,3-dioxol-2-on-4-ylmethyl group).

As the more preferred compound of the present invention, there is a compound of the formula (I), wherein A is a carbon atom; n is 1; R^1 is



(wherein D and E independently indicate a single bond or an optionally branched C_1-C_6 alkylene group;

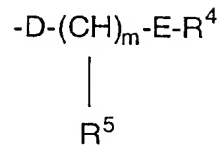
R^4 is a C_1-C_6 alkyl group; -OR^6 (R^6 is a C_6-C_{10} aryl or C_7-C_{12} aralkyl group which may be substituted with at least one substituent selected from the group consisting of a C_1-C_6 alkyl group, a halogen atom, a carboxyl group, a C_2-C_7 carboxyalkyl group and a benzyloxycarbonyl group); -SR^7 (R^7 is a C_1-C_6 alkyl group); a C_6-C_{10} aryl group which may be substituted with at least one substituent selected from the group consisting of a C_1-C_6 alkyl group, a halogen atom, a carboxyl group, a C_2-C_7 carboxyalkyl group and a benzyloxycarbonyl group; or a C_3-C_6 cycloalkyl group;

R^5 is -OH, -NH_2, -$NHCOR^{20}$ (R^{20} is a C_1-C_6 alkoxy group or a C_7-C_{12} aralkyloxy group) or -$NHSO_2R^{21}$ (R^{21} is a C_1-C_6 alkyl group or a C_6-C_{10} aryl group);
and m is 1};

R^2 is a hydrogen atom; and

R^3 is -$C(=NR^{25})NH_2$ (R^{25} is a hydrogen atom or a hydroxyl group) or -NH_2.

As the more preferred compound of the present invention, there is a compound of the formula (I), wherein A is a carbon atom; n is 1; R^1 is



{wherein D is a single bond and E is a single bond or a C_1-C_6 alkylene group;

R^4 is a C_1-C_6 alkyl group; -OR^6 (R^6 is a C_6-C_{10} aryl or C_7-C_{12} aralkyl group which may be substituted with at least one substituent selected from the group consisting of a C_1-C_6 alkyl group, a halogen atom, a carboxyl group, a C_2-C_7 carboxyalkyl group and a benzyloxycarbonyl group); -SR^7 (R^7 is a C_1-C_6 alkyl group); a C_6-C_{10} aryl group which may be substituted with at least one substituent selected from the group consisting of a C_1-C_6 alkyl group, a halogen atom, a carboxyl group, a C_2-C_7 carboxyalkyl group and a benzyloxycarbonyl group; or a C_3-C_6 cycloalkyl group;

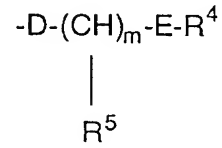
R^5 is -NH_2, -$NHCOR^{20}$ (R^{20} is a C_1-C_6 alkoxy group or a C_7-C_{12} aralkyloxy group) or -$NHSO_2R^{21}$ (R^{21} is a C_1-C_6 alkyl group or a C_6-C_{10} aryl group);

and m is 1};

R^2 is a hydrogen atom; and

R^3 is -$C(=NR^{25})NH_2$ (R^{25} is a hydrogen atom or a hydroxyl group) or -NH_2.

As the still more preferred compound of the present invention, there is a compound of the formula (I), wherein A is a carbon atom; n is 1; R^1 is

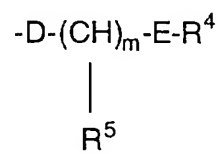


{wherein D is a single bond; E is a single bond or a C_1-C_3 alkylene group; R^4 is a C_3-C_6 alkyl group, -OR^6 (R^6 is a C_1-C_6 alkyl group), a phenyl group or a C_3-C_6 cycloalkyl group; R^5 is -OH, -NHR^{19} (R^{19} is a hydrogen atom), - $NHCOR^{20}$ (R^{20} is a C_1-C_6 alkoxy group) or -$NHSO_2R^{21}$ (R^{21} is a C_1-C_3 alkyl group); and m is 1};

R^2 is a hydrogen atom; and

R^3 is -$C(=NR^{25})NH_2$ (R^{25} is a hydrogen atom or a hydroxyl group) or -NH_2.

As the particularly preferred compound of the present invention, there is a compound of the formula (I), wherein A is a carbon atom; n is 1; R^1 is



{wherein D is a single bond; E is a single bond or a C_1-C_6 alkylene group; R^4 is a C_1-C_6 alkyl group; R^5 is -$NHCOR^{20}$ (R^{20} is a C_1-C_6 alkoxy group); and m is 1};

R^2 is a hydrogen atom; and

R^3 is -$C(=NR^{25})NH_2$ (R^{25} is a hydrogen atom or a hydroxyl group)).

As the most preferred compound of the present invention, there is trans-4-[(S)-N-((R)-2-ethoxycarbonylamino-4,4-dimethylpentanoyl) prolyl] aminomethylcyclohexanecarboxamidoxime (compound No. 461 in Table 1 in Example 33).

The prolineamide derivatives represented by the above formula (I) can afford various stereoisomers. For example, concerning asymmetric carbon atoms, the absolute configuration may be D-configuration, L-configuration or DL configuration and all types thereof are included in the compounds of the present invention.

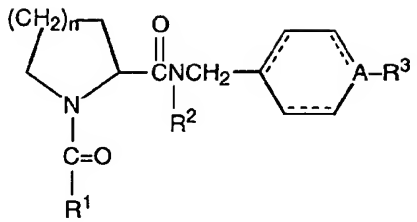
Examples of the salt which can be formed with the compounds of the above formula (I) of the present invention include inorganic acid salts such as hydrochloride, hydrobromide, hydroiodide, sulfate, nitrate, phosphate, etc.; organic acid salts such as succinate, oxalate, fumarate, maleate, lactate, tartrate, citrate, acetate, glycolate, methanesulfonate, toluenesulfonate, etc. Further, the proline derivatives of the above formula (I) containing a free carboxyl group can also form a salt with a pharmaceutically acceptable base.

Examples of the salt include alkaline metal salt, alkaline earth metal salt, ammonium salt, alkyl ammonium salt and the like.

Further, the prolineamide derivatives of the above formula (I) and the salts thereof can also form a hydrate.

Hereinafter, examples of the compounds of the present invention will be described.

Table 1



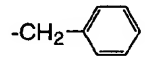
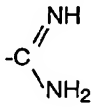
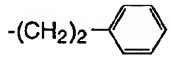
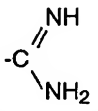
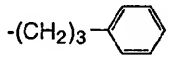
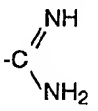
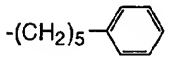
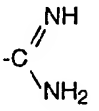
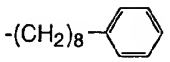
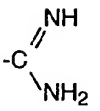
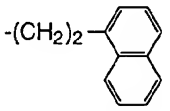
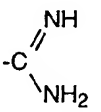
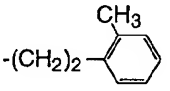
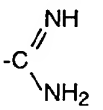
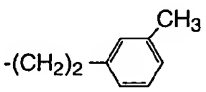
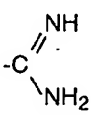
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
1		-H		1	C	Single bond
2		-H		1	C	Single bond
3		-H		1	C	Single bond
4		-H		1	C	Single bond
5		-H		1	C	Single bond
6		-H		1	C	Single bond
7		-H		1	C	Single bond
8		-H		1	C	Single bond

Table 1 (continued)

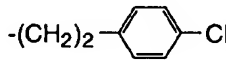
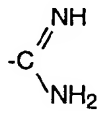
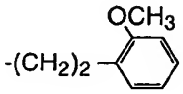
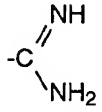
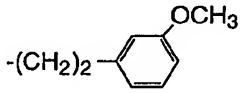
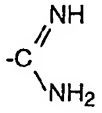
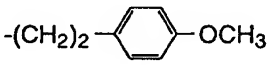
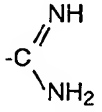
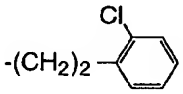
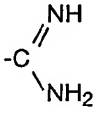
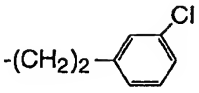
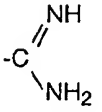
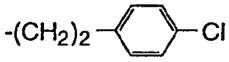
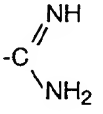
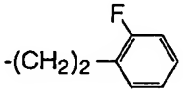
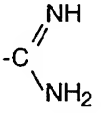
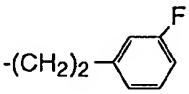
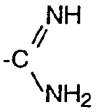
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
9		-H		1	C	Single bond
10		-H		1	C	Single bond
11		-H		1	C	Single bond
12		-H		1	C	Single bond
13		-H		1	C	Single bond
14		-H		1	C	Single bond
15		-H		1	C	Single bond
16		-H		1	C	Single bond
17		-H		1	C	Single bond

Table 1 (continued)

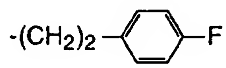
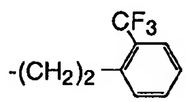
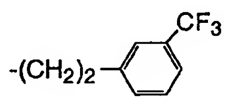
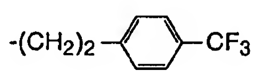
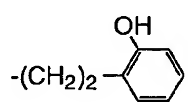
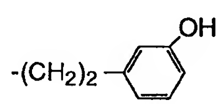
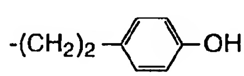
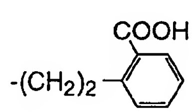
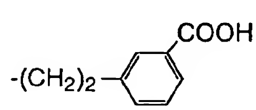
Compound No.	$-R^1\left(\begin{array}{c}-D-(CH)_m-E-R^4 \\ \vert \\ R^5\end{array}\right)$	$-R^2$	$-R^3$	n	A	Broken line
18		-H	$-C(=NH)NH_2$	1	C	Single bond
19		-H	$-C(=NH)NH_2$	1	C	Single bond
20		-H	$-C(=NH)NH_2$	1	C	Single bond
21		-H	$-C(=NH)NH_2$	1	C	Single bond
22		-H	$-C(=NH)NH_2$	1	C	Single bond
23		-H	$-C(=NH)NH_2$	1	C	Single bond
24		-H	$-C(=NH)NH_2$	1	C	Single bond
25		-H	$-C(=NH)NH_2$	1	C	Single bond
26		-H	$-C(=NH)NH_2$	1	C	Single bond

Table 1 (continued)

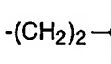
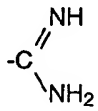
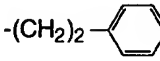
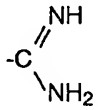
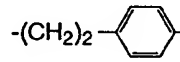
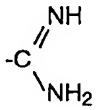
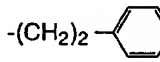
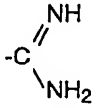
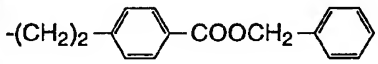
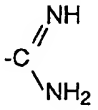
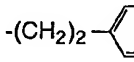
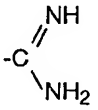
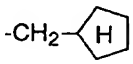
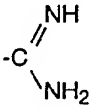
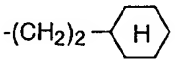
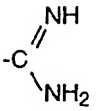
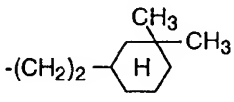
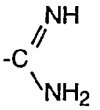
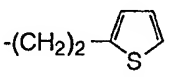
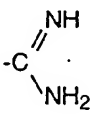
Compound No.	$-R^1\left(-D-(CH)_m-E-R^4 \atop R^5\right)$	$-R^2$	$-R^3$	n	A	Broken line
27		-H		1	C	Single bond
28		-H		1	C	Single bond
29		-H		1	C	Single bond
30		-H		1	C	Single bond
31		-H		1	C	Single bond
32		-H		1	C	Single bond
33		-H		1	C	Single bond
34		-H		1	C	Single bond
35		-H		1	C	Single bond
36		-H		1	C	Single bond

Table 1 (continued)

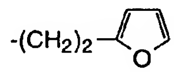
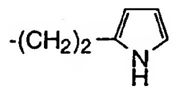
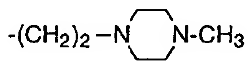
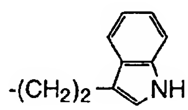
Compound No.	$-R^1\left(\begin{array}{c}-D-(CH)_m-E-R^4\\ \mid \\ R^5\end{array}\right)$	$-R^2$	$-R^3$	n	A	Broken line
37		-H	$-C(=NH)NH_2$	1	C	Single bond
38		-H	$-C(=NH)NH_2$	1	C	Single bond
39		-H	$-C(=NH)NH_2$	1	C	Single bond
40		-H	$-C(=NH)NH_2$	1	C	Single bond
41	$-CH_3$	-H	$-C(=NH)NH_2$	1	C	Single bond
42	$-CH_2CH_3$	-H	$-C(=NH)NH_2$	1	C	Single bond
43	$-(CH_2)_2CH_3$	-H	$-C(=NH)NH_2$	1	C	Single bond
44	$-CH(CH_3)_2$	-H	$-C(=NH)NH_2$	1	C	Single bond
45	$-(CH_2)_3CH_3$	-H	$-C(=NH)NH_2$	1	C	Single bond
46	$-C(CH_3)_3$	-H	$-C(=NH)NH_2$	1	C	Single bond

Table 1 (continued)

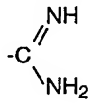
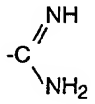
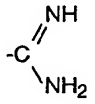
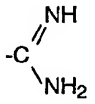
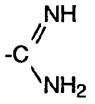
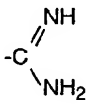
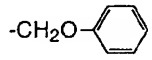
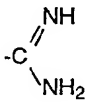
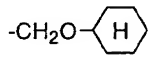
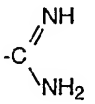
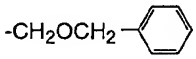
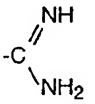
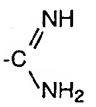
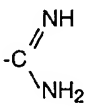
Compound No.	$-R^1\left(-D-(CH)_m-E-R^4 \atop R^5\right)$	$-R^2$	$-R^3$	n	A	Broken line
47	$-(CH_2)_4CH_3$	-H		1	C	Single bond
48	$-CH_2CH_2C(CH_3)_3$	-H		1	C	Single bond
49	$-(CH_2)_9CH_3$	-H		1	C	Single bond
50	$-CH_2Si(CH_3)_3$	-H		1	C	Single bond
51	$-CH_2CH_2Si(CH_3)_3$	-H		1	C	Single bond
52	$-CH_2OCH_3$	-H		1	C	Single bond
53		-H		1	C	Single bond
54		-H		1	C	Single bond
55		-H		1	C	Single bond
56	$-CH_2OH$	-H		1	C	Single bond
57	$-CH_2SCH_3$	-H		1	C	Single bond

Table 1 (continued)

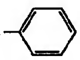
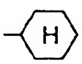
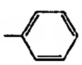
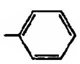
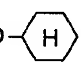
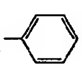
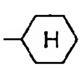
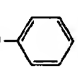
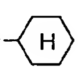
Compound No.	$-R^1\left(-D-(\underset{R^5}{CH})_m-E-R^4\right)$	$-R^2$	$-R^3$	n	A	Broken line
58	$-CH_2S-$ 	-H	$-C(=NH)NH_2$	1	C	Single bond
59	$-CH_2S-$ 	-H	$-C(=NH)NH_2$	1	C	Single bond
60	$-CH_2SCH_2-$ 	-H	$-C(=NH)NH_2$	1	C	Single bond
61	$-CH_2SO-$ 	-H	$-C(=NH)NH_2$	1	C	Single bond
62	$-CH_2SO-$ 	-H	$-C(=NH)NH_2$	1	C	Single bond
63	$-CH_2SO_2-$ 	-H	$-C(=NH)NH_2$	1	C	Single bond
64	$-CH_2SO_2-$ 	-H	$-C(=NH)NH_2$	1	C	Single bond
65	$-CH_2CO-$ 	-H	$-C(=NH)NH_2$	1	C	Single bond
66	$-CH_2CO-$ 	-H	$-C(=NH)NH_2$	1	C	Single bond
67	$-CH_2COOH$	-H	$-C(=NH)NH_2$	1	C	Single bond
68	$-CH_2COOCH_3$	-H	$-C(=NH)NH_2$	1	C	Single bond

Table 1 (continued)

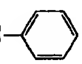
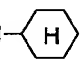
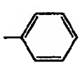
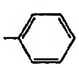
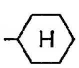
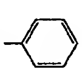
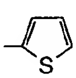
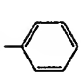
Compound No.	$-R^1\left(\begin{array}{c}-D-(\underset{\substack{\vert\\ R^5}}{CH})_m-E-R^4\end{array}\right)$	$-R^2$	$-R^3$	n	A	Broken line
69	$-CH_2NHCH_3$	-H	$-C(=NH)NH_2$	1	C	Single bond
70	$-CH_2NH-$ 	-H	$-C(=NH)NH_2$	1	C	Single bond
71	$-CH_2NH-$ 	-H	$-C(=NH)NH_2$	1	C	Single bond
72	$-CH_2NHCH_2-$ 	-H	$-C(=NH)NH_2$	1	C	Single bond
73	$-CH_2NHCOOCH_3$	-H	$-C(=NH)NH_2$	1	C	Single bond
74	$-CH_2NHCO-$ 	-H	$-C(=NH)NH_2$	1	C	Single bond
75	$-CH_2NHCO-$ 	-H	$-C(=NH)NH_2$	1	C	Single bond
76	$-CH_2NHCOOCH_2-$ 	-H	$-C(=NH)NH_2$	1	C	Single bond
77	$-CH_2NHSO_2-$ 	-H	$-C(=NH)NH_2$	1	C	Single bond
78	$-CH_2NHSO_2CH_3$	-H	$-C(=NH)NH_2$	1	C	Single bond
79	$-CH_2NHSO_2-$ 	-H	$-C(=NH)NH_2$	1	C	Single bond

Table 1 (continued)

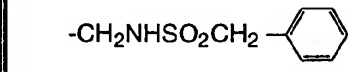
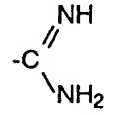
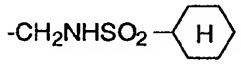
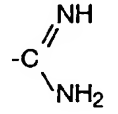
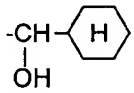
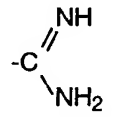
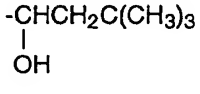
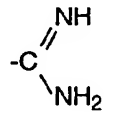
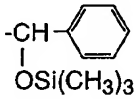
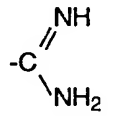
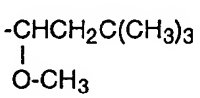
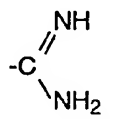
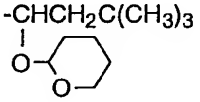
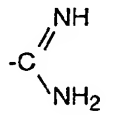
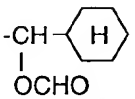
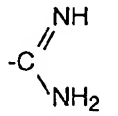
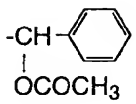
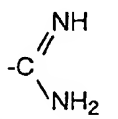
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \vert\\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
80		-H		1	C	Single bond
81		-H		1	C	Single bond
82		-H		1	C	Single bond
83		-H		1	C	Single bond
84		-H		1	C	Single bond
85		-H		1	C	Single bond
86		-H		1	C	Single bond
87		-H		1	C	Single bond
88		-H		1	C	Single bond

Table 1 (continued)

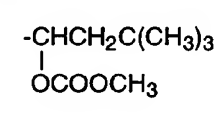
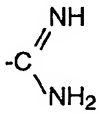
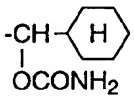
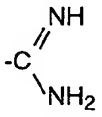
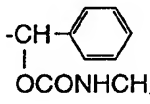
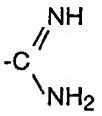
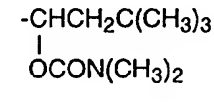
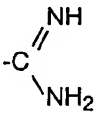
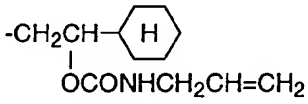
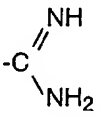
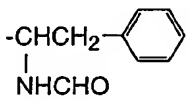
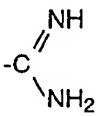
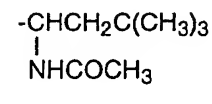
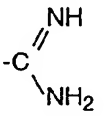
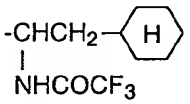
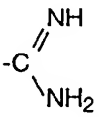
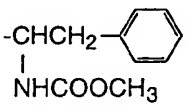
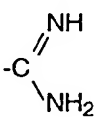
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
89		-H		1	C	Single bond
90		-H		1	C	Single bond
91		-H		1	C	Single bond
92		-H		1	C	Single bond
93		-H		1	C	Single bond
94		-H		1	C	Single bond
95		-H		1	C	Single bond
96		-H		1	C	Single bond
97		-H		1	C	Single bond

Table 1 (continued)

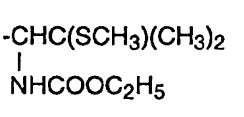
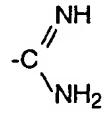
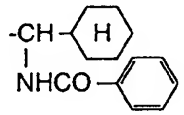
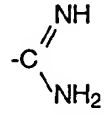
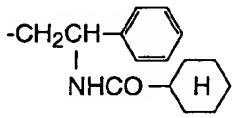
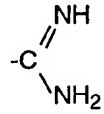
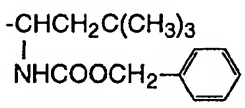
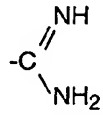
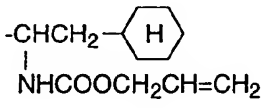
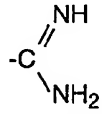
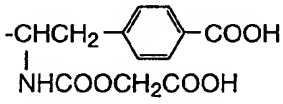
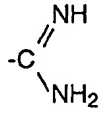
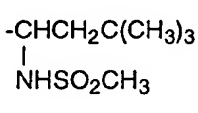
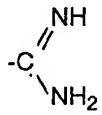
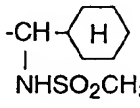
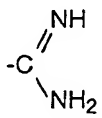
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
98		-H		1	C	Single bond
99		-H		1	C	Single bond
100		-H		1	C	Single bond
101		-H		1	C	Single bond
102		-H		1	C	Single bond
103		-H		1	C	Single bond
104		-H		1	C	Single bond
105		-H		1	C	Single bond

Table 1 (continued)

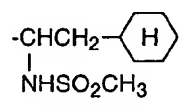
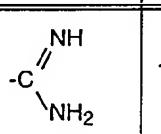
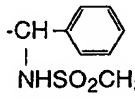
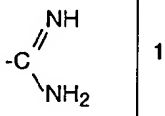
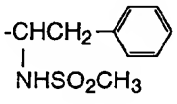
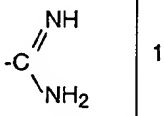
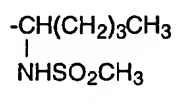
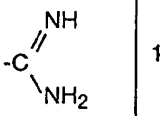
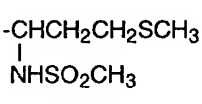
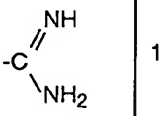
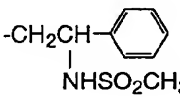
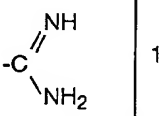
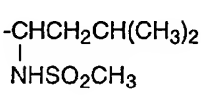
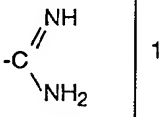
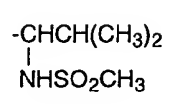
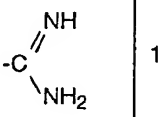
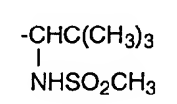
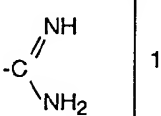
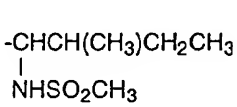
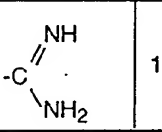
Compound No.	$-R^1\left(-D-(CH)_m-E-R^4\right)$ with R^5	$-R^2$	$-R^3$	n	A	Broken line
106		-H		1	C	Single bond
107		-H		1	C	Single bond
108		-H		1	C	Single bond
109		-H		1	C	Single bond
110		-H		1	C	Single bond
111		-H		1	C	Single bond
112		-H		1	C	Single bond
113		-H		1	C	Single bond
114		-H		1	C	Single bond
115		-H		1	C	Single bond

Table 1 (continued)

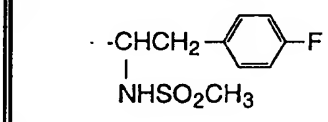
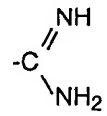
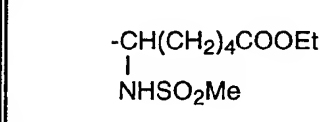
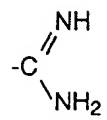
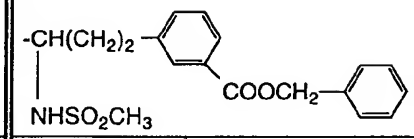
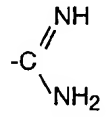
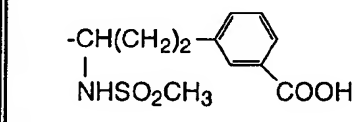
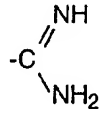
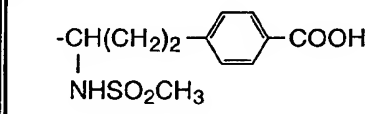
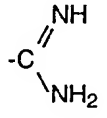
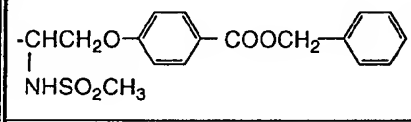
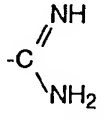
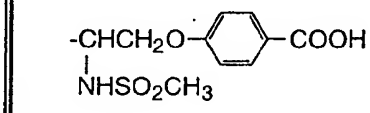
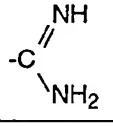
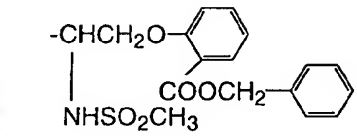
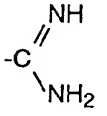
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
116		-H		1	C	Single bond
117		-H		1	C	Single bond
118		-H		1	C	Single bond
119		-H		1	C	Single bond
120		-H		1	C	Single bond
121		-H		1	C	Single bond
122		-H		1	C	Single bond
123		-H		1	C	Single bond

Table 1 (continued)

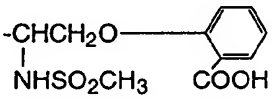
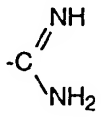
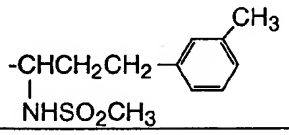
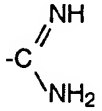
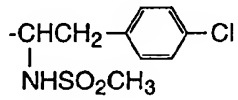
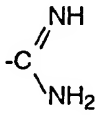
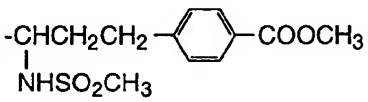
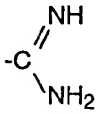
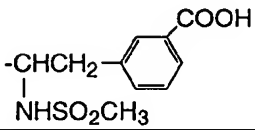
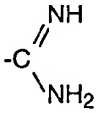
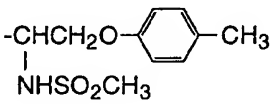
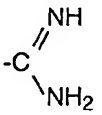
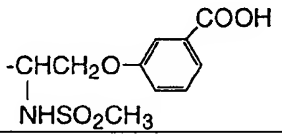
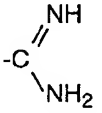
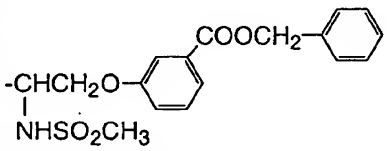
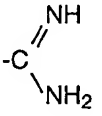
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
124		-H		1	C	Single bond
125		-H		1	C	Single bond
126		-H		1	C	Single bond
127		-H		1	C	Single bond
128		-H		1	C	Single bond
129		-H		1	C	Single bond
130		-H		1	C	Single bond
131		-H		1	C	Single bond

Table 1 (continued)

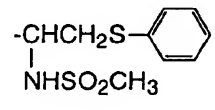
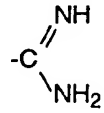
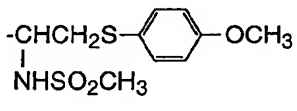
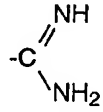
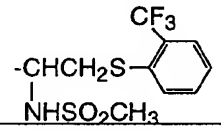
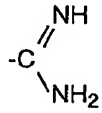
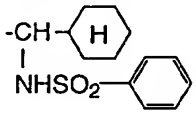
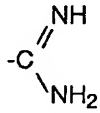
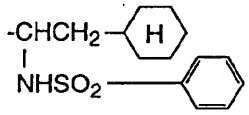
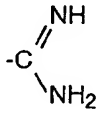
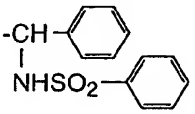
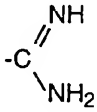
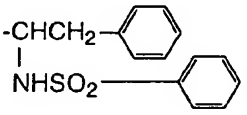
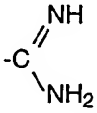
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
132		-H		1	C	Single bond
133		-H		1	C	Single bond
134		-H		1	C	Single bond
135		-H		1	C	Single bond
136		-H		1	C	Single bond
137		-H		1	C	Single bond
138		-H		1	C	Single bond

Table 1 (continued)

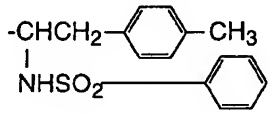
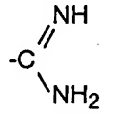
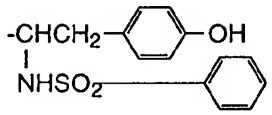
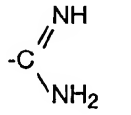
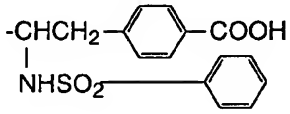
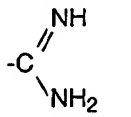
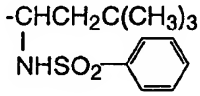
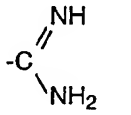
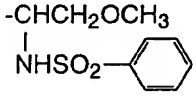
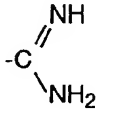
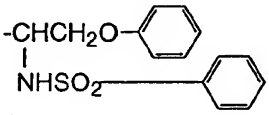
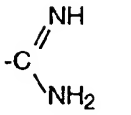
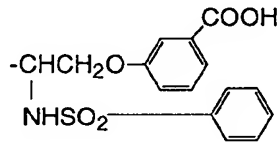
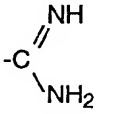
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
139		-H		1	C	Single bond
140		-H		1	C	Single bond
141		-H		1	C	Single bond
142		-H		1	C	Single bond
143		-H		1	C	Single bond
144		-H		1	C	Single bond
145		-H		1	C	Single bond

Table 1 (continued)

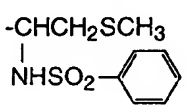
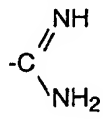
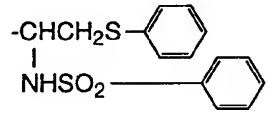
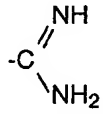
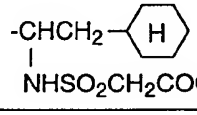
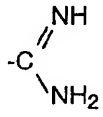
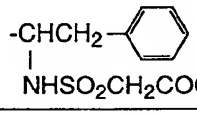
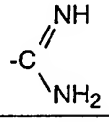
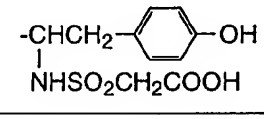
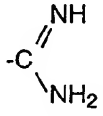
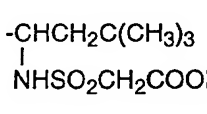
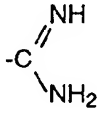
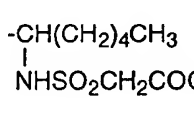
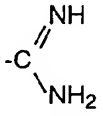
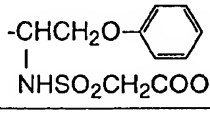
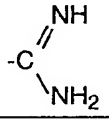
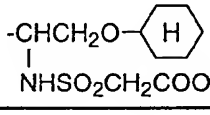
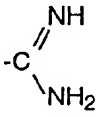
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
146		-H		1	C	Single bond
147		-H		1	C	Single bond
148		-H		1	C	Single bond
149		-H		1	C	Single bond
150		-H		1	C	Single bond
151		-H		1	C	Single bond
152		-H		1	C	Single bond
153		-H		1	C	Single bond
154		-H		1	C	Single bond

Table 1 (continued)

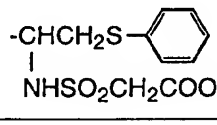
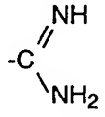
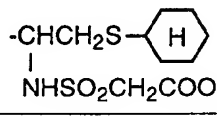
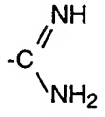
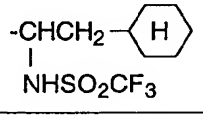
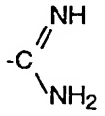
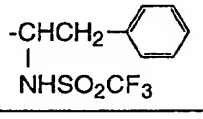
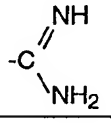
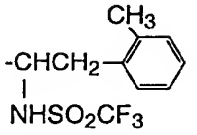
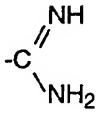
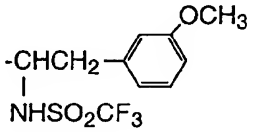
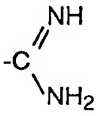
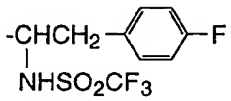
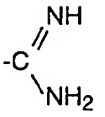
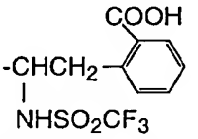
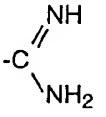
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
155		-H		1	C	Single bond
156		-H		1	C	Single bond
157		-H		1	C	Single bond
158		-H		1	C	Single bond
159		-H		1	C	Single bond
160		-H		1	C	Single bond
161		-H		1	C	Single bond
162		-H		1	C	Single bond

Table 1 (continued)

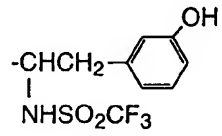
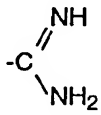
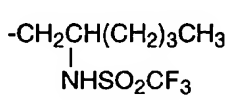
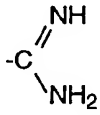
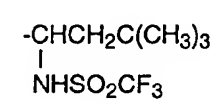
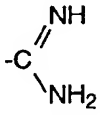
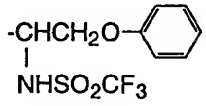
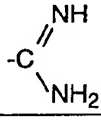
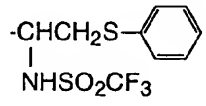
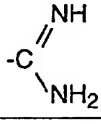
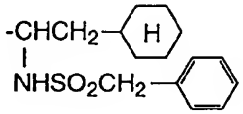
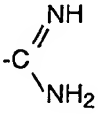
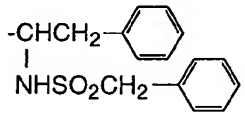
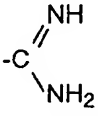
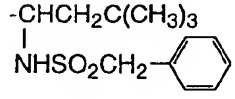
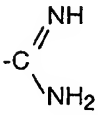
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
163		-H		1	C	Single bond
164		-H		1	C	Single bond
165		-H		1	C	Single bond
166		-H		1	C	Single bond
167		-H		1	C	Single bond
168		-H		1	C	Single bond
169		-H		1	C	Single bond
170		-H		1	C	Single bond

Table 1 (continued)

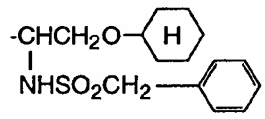
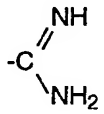
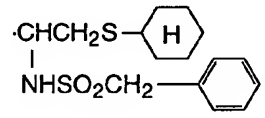
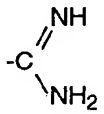
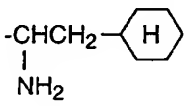
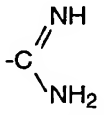
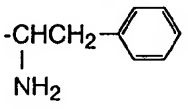
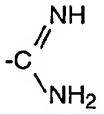
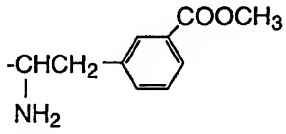
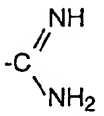
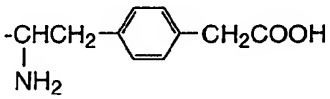
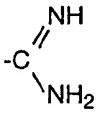
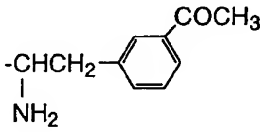
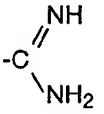
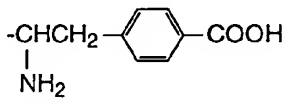
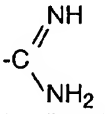
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
171		-H		1	C	Single bond
172		-H		1	C	Single bond
173		-H		1	C	Single bond
174		-H		1	C	Single bond
175		-H		1	C	Single bond
176		-H		1	C	Single bond
177		-H		1	C	Single bond
178		-H		1	C	Single bond

Table 1 (continued)

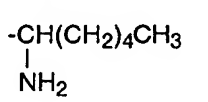
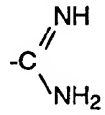
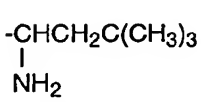
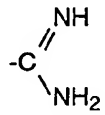
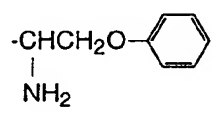
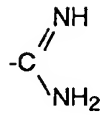
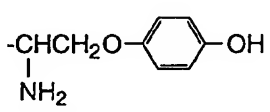
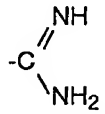
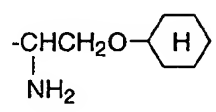
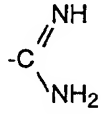
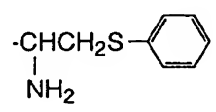
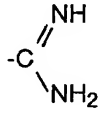
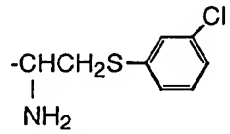
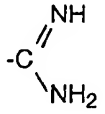
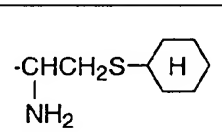
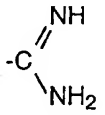
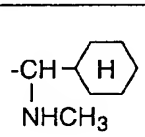
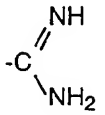
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
179		-H		1	C	Single bond
180		-H		1	C	Single bond
181		-H		1	C	Single bond
182		-H		1	C	Single bond
183		-H		1	C	Single bond
184		-H		1	C	Single bond
185		-H		1	C	Single bond
186		-H		1	C	Single bond
187		-H		1	C	Single bond

Table 1 (continued)

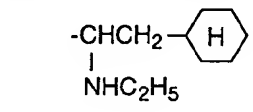
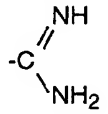
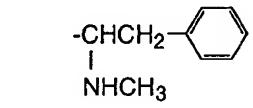
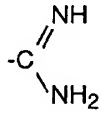
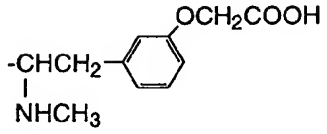
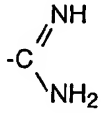
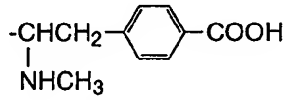
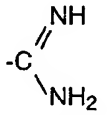
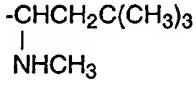
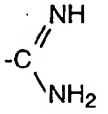
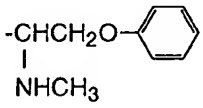
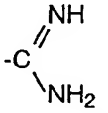
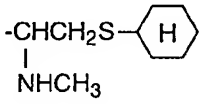
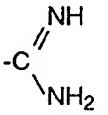
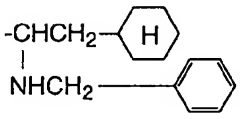
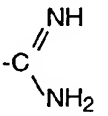
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
188		-H		1	C	Single bond
189		-H		1	C	Single bond
190		-H		1	C	Single bond
191		-H		1	C	Single bond
192		-H		1	C	Single bond
193		-H		1	C	Single bond
194		-H		1	C	Single bond
195		-H		1	C	Single bond

Table 1 (continued)

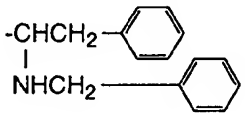
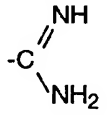
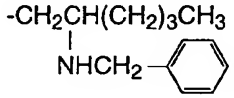
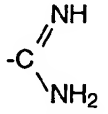
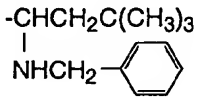
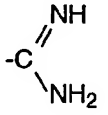
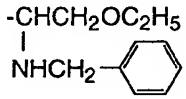
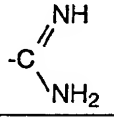
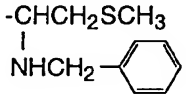
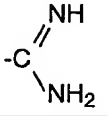
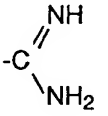
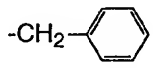
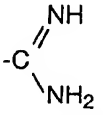
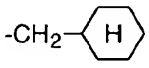
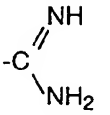
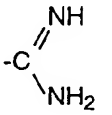
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
196		-H		1	C	Single bond
197		-H		1	C	Single bond
198		-H		1	C	Single bond
199		-H		1	C	Single bond
200		-H		1	C	Single bond
201		-H		1	C	——
202		-H		1	C	——
203		-H		1	C	——
204	$-(CH_2)_2CH_3$	-H		1	C	——

Table 1 (continued)

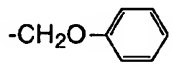
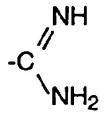
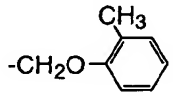
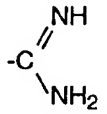
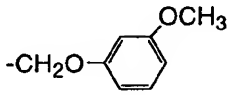
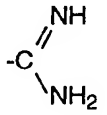
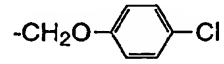
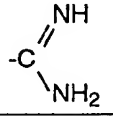
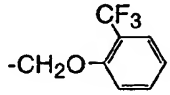
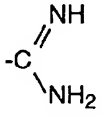
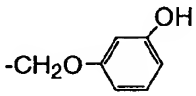
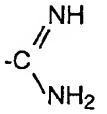
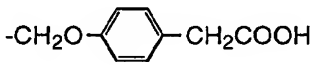
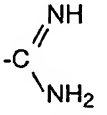
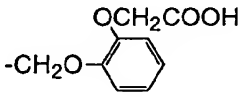
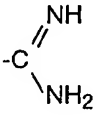
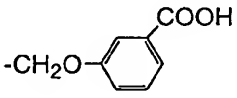
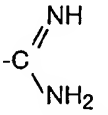
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	-R2	-R3	n	A	Broken line
205		-H		1	C	——
206		-H		1	C	——
207		-H		1	C	——
208		-H		1	C	——
209		-H		1	C	——
210		-H		1	C	——
211		-H		1	C	——
212		-H		1	C	——
213		-H		1	C	——

Table 1 (continued)

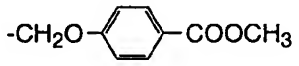
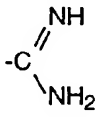
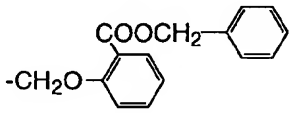
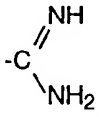
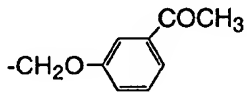
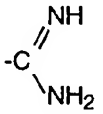
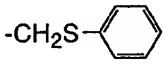
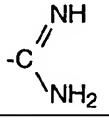
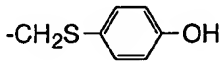
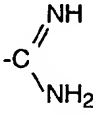
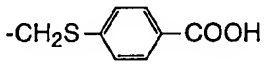
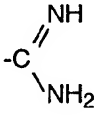
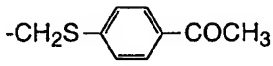
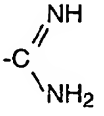
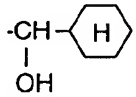
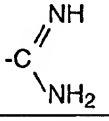
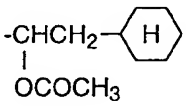
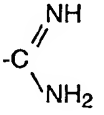
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
214		-H		1	C	——
215		-H		1	C	——
216		-H		1	C	——
217		-H		1	C	——
218		-H		1	C	——
219		-H		1	C	——
220		-H		1	C	——
221		-H		1	C	——
222		-H		1	C	——

Table 1 (continued)

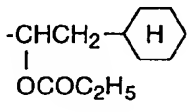
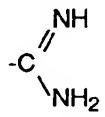
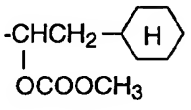
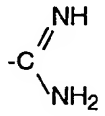
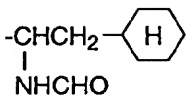
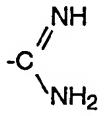
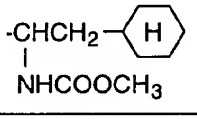
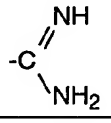
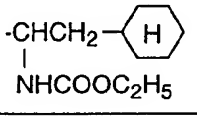
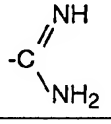
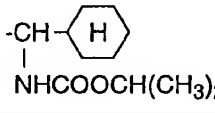
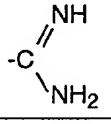
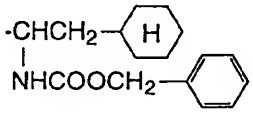
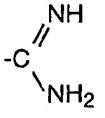
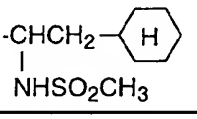
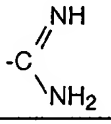
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \vert\\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
223		-H		1	C	——
224		-H		1	C	——
225		-H		1	C	——
226		-H		1	C	——
227		-H		1	C	——
228		-H		1	C	——
229		-H		1	C	——
230		-H		1	C	——

Table 1 (continued)

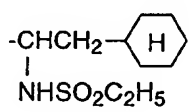
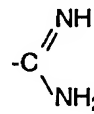
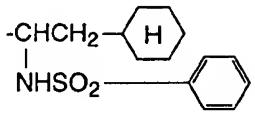
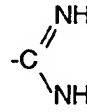
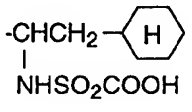
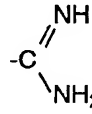
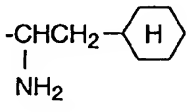
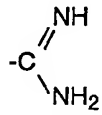
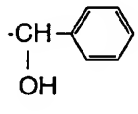
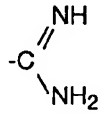
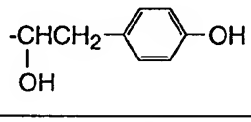
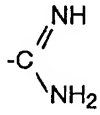
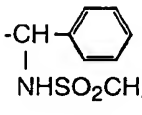
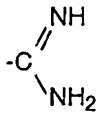
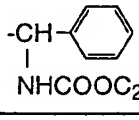
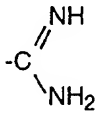
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
231		-H		1	C	——
232		-H		1	C	——
233		-H		1	C	——
234		-H		1	C	——
235		-H		1	C	——
236		-H		1	C	——
237		-H		1	C	——
238		-H		1	C	——

Table 1 (continued)

Compound No.	$-R^1\left(-D-(CH)_m-E-R^4 \atop R^5\right)$	$-R^2$	$-R^3$	n	A	Broken line
239	$-CHCH_2C(CH_3)_3$ $NHSO_2CH_3$	-H	$-C(=NH)-NH_2$	1	C	——
240	$-CHCH_2OC(CH_3)_3$ $NHCOOC_2H_5$	-H	$-C(=NH)-NH_2$	1	C	——
241	$-CHCH(CH_3)_2$ $NHSO_2CH_3$	-H	$-C(=NH)-NH_2$	1	C	——
242	$-CHCH(CH_3)_2$ $NHCOOC_2H_5$	-H	$-C(=NH)-NH_2$	1	C	——
243	$-CHC(CH_3)_3$ $NHSO_2CH_3$	-H	$-C(=NH)-NH_2$	1	C	——
244	$-CHC(CH_3)_3$ $NHCOOC_2H_5$	-H	$-C(=NH)-NH_2$	1	C	——
245	$-CH(CH_2)_3CH_3$ $NHSO_2CH_3$	-H	$-C(=NH)-NH_2$	1	C	——
246	$-CHCH_2CH_2SCH_3$ $NHSO_2CH_3$	-H	$-C(=NH)-NH_2$	1	C	——

Table 1 (continued)

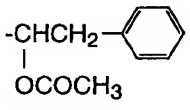
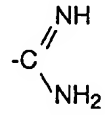
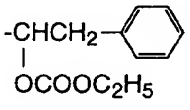
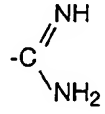
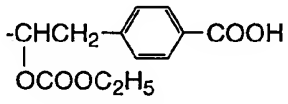
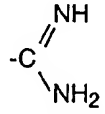
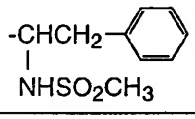
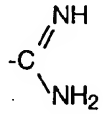
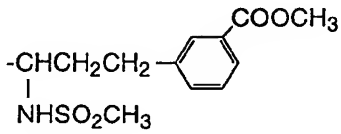
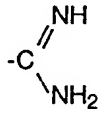
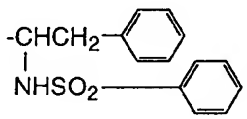
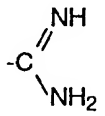
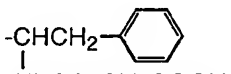
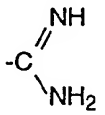
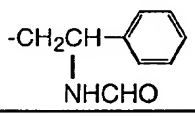
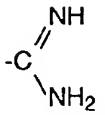
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
247		-H		1	C	——
248		-H		1	C	——
249		-H		1	C	——
250		-H		1	C	——
251		-H		1	C	——
252		-H		1	C	——
253		-H		1	C	——
254		-H		1	C	——

Table 1 (continued)

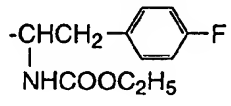
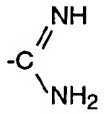
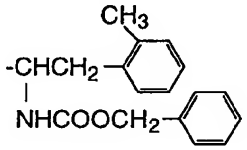
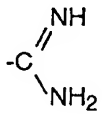
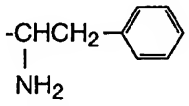
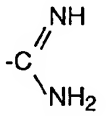
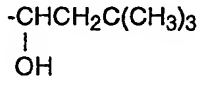
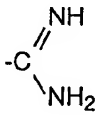
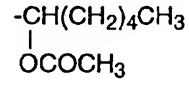
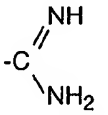
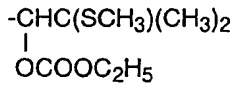
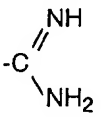
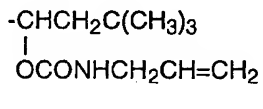
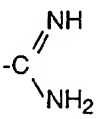
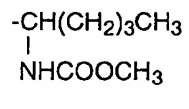
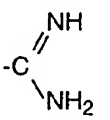
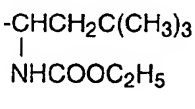
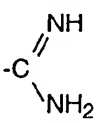
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
255		-H		1	C	——
256		-H		1	C	——
257		-H		1	C	——
258		-H		1	C	——
259		-H		1	C	——
260		-H		1	C	——
261		-H		1	C	——
262		-H		1	C	——
263		-H		1	C	——

Table 1 (continued)

Compound No.	$-R^1\left(-D-(CH)_m-E-R^4, R^5\right)$	$-R^2$	$-R^3$	n	A	Broken line
264	$-CHCH_2CH(C_2H_5)_2$, $NHCOOC_2H_5$	-H	$-C(=NH)-NH_2$	1	C	——
265	$-CHCH_2C(CH_3)_3$, $NHCOOCH(CH_3)_2$	-H	$-C(=NH)-NH_2$	1	C	——
266	$-CHCH_2C(CH_3)_3$, $NHCOOC(CH_3)_3$	-H	$-C(=NH)-NH_2$	1	C	——
267	$-CH(CH_2)_4CH_3$, $NHCOOCH_2-C_6H_5$	-H	$-C(=NH)-NH_2$	1	C	——
268	$-CH_2CH(CH_2)_2CH_3$, $NHSO_2CH_3$	-H	$-C(=NH)-NH_2$	1	C	——
269	$-CHCH_2CH(CH_3)_2$, $NHSO_2CH_3$	-H	$-C(=NH)-NH_2$	1	C	——
270	$-CHCH_2C(CH_3)_3$, $NHSO_2-C_6H_5$	-H	$-C(=NH)-NH_2$	1	C	——
271	$-CH_2CH(CH_2)_2CH_3$, NH_2	-H	$-C(=NH)-NH_2$	1	C	——
272	$-(CH_2)_2-C_6H_5$	-H	$-C(=NH)-NH_2$	1	N	——
273	$-CH_2OCH_2-C_6H_5$	-H	$-C(=NH)-NH_2$	1	N	——

Table 1 (continued)

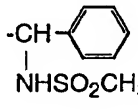
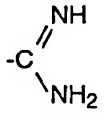
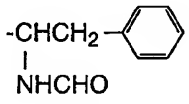
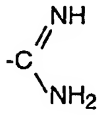
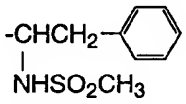
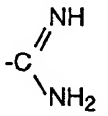
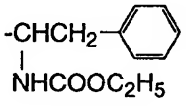
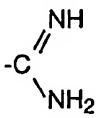
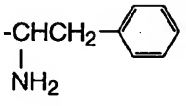
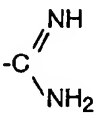
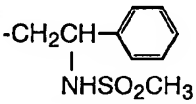
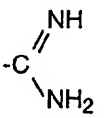
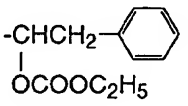
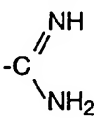
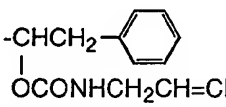
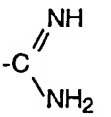
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
274		-H		1	N	——
275		-H		1	N	——
276		-H		1	N	——
277		-H		1	N	——
278		-H		1	N	——
279		-H		1	N	——
280		-H		1	N	——
281		-H		1	N	——

Table 1 (continued)

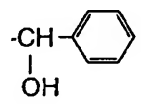
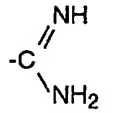
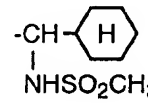
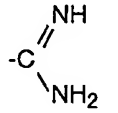
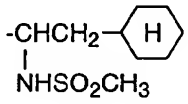
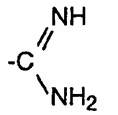
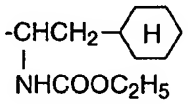
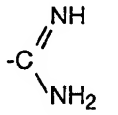
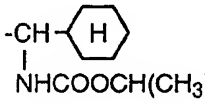
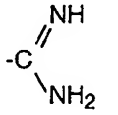
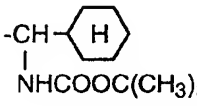
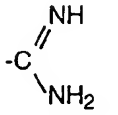
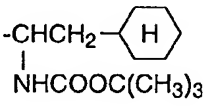
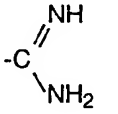
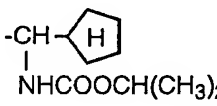
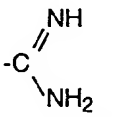
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
282		-H		1	N	——
283		-H		1	N	——
284		-H		1	N	——
285		-H		1	N	——
286		-H		1	N	——
287		-H		1	N	——
288		-H		1	N	——
289		-H		1	N	——

Table 1 (continued)

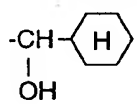
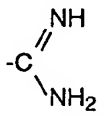
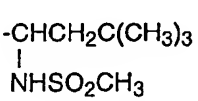
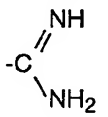
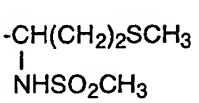
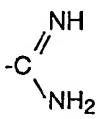
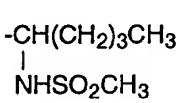
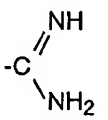
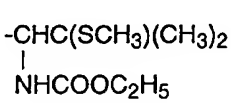
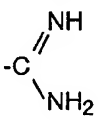
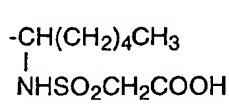
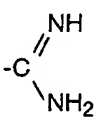
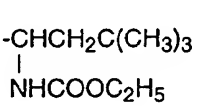
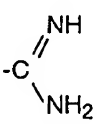
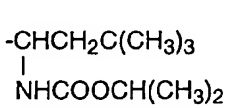
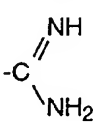
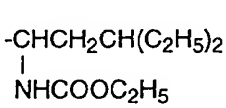
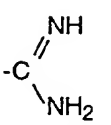
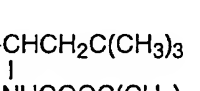
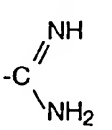
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
290		-H		1	N	——
291		-H		1	N	——
292		-H		1	N	——
293		-H		1	N	——
294		-H		1	N	——
295		-H		1	N	——
296		-H		1	N	——
297		-H		1	N	——
298		-H		1	N	——
299		-H		1	N	——

Table 1 (continued)

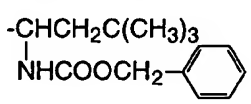
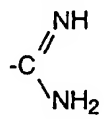
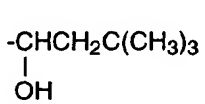
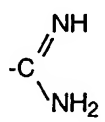
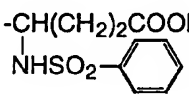
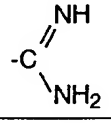
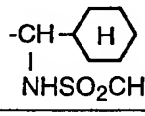
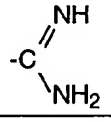
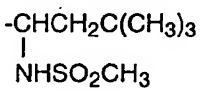
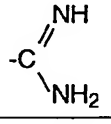
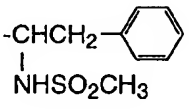
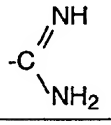
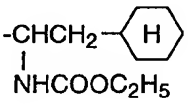
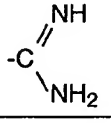
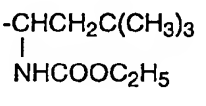
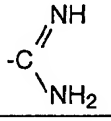
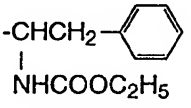
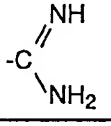
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
300		-H		1	N	——
301		-H		1	N	——
302		-H		1	N	——
303		-H		2	C	Single bond
304		-H		2	C	Single bond
305		-H		2	C	Single bond
306		-H		2	C	Single bond
307		-H		2	C	Single bond
308		-H		2	C	Single bond

Table 1 (continued)

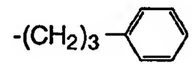
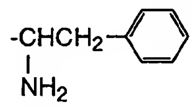
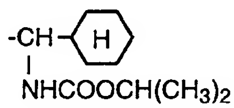
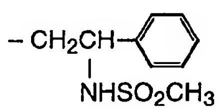
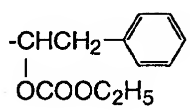
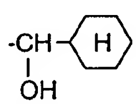
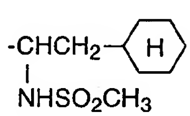
Compound No.	$-R^1\left(-D-(\underset{\mid}{CH}R^5)_m-E-R^4\right)$	$-R^2$	$-R^3$	n	A	Broken line
309		-H	$-C(=NH)NH_2$	2	C	Single bond
310		-H	$-C(=NH)NH_2$	2	C	Single bond
311		-H	$-C(=NH)NH_2$	2	C	Single bond
312	$-CH(NHCOOC(CH_3)_3)CH_2C(C_2H_5)_2$	-H	$-C(=NH)NH_2$	2	C	Single bond
313	$-CH(OH)CH_2C(CH_3)_3$	-H	$-C(=NH)NH_2$	2	C	Single bond
314		-H	$-C(=NH)NH_2$	2	C	Single bond
315		-H	$-C(=NH)NH_2$	2	C	Single bond
316		-H	$-C(=NH)NH_2$	2	C	Single bond
317		-H	$-C(=NH)NH_2$	2	C	——

Table 1 (continued)

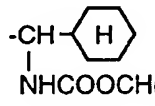
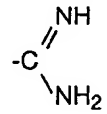
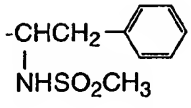
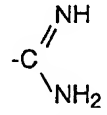
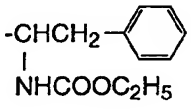
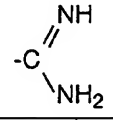
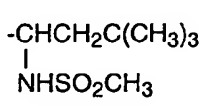
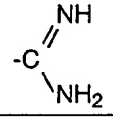
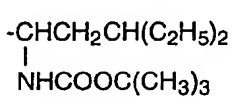
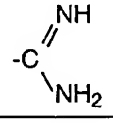
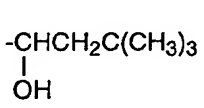
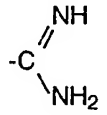
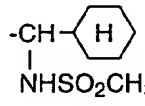
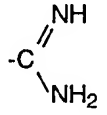
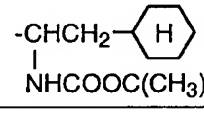
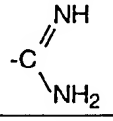
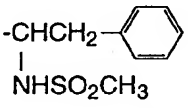
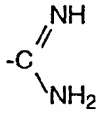
Compound No.	$-R^1\left(-D-(CH)_m-E-R^4 \atop R^5\right)$	$-R^2$	$-R^3$	n	A	Broken line
318		-H		2	C	——
319		-H		2	C	——
320		-H		2	C	——
321		-H		2	C	——
322		-H		2	C	——
323		-H		2	C	——
324		-H		2	N	——
325		-H		2	N	——
326		-H		2	N	——

Table 1 (continued)

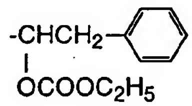
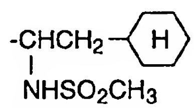
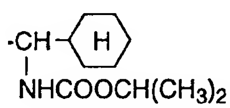
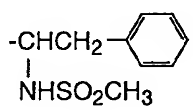
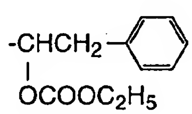
Compound No.	$-R^1\left(\begin{array}{c}-D-(CH)_m-E-R^4\\ \mid \\ R^5\end{array}\right)$	$-R^2$	$-R^3$	n	A	Broken line
327		-H	$-C(=NH)NH_2$	2	N	——
328	$-CHCH_2C(CH_3)_3$ with $NHSO_2CH_3$ on the CH	-H	$-C(=NH)NH_2$	2	N	——
329	$-CH(CH_2)_2SCH_3$ with $NHCOOCH(CH_3)_2$ on the CH	-H	$-C(=NH)NH_2$	2	N	——
330	$-CHCH_2C(CH_3)_3$ with OH on the CH	-H	$-C(=NH)NH_2$	2	N	——
331		$-CH_3$	$-C(=NH)NH_2$	1	C	Single bond
332		$-CH_3$	$-C(=NH)NH_2$	1	C	Single bond
333		$-CH_3$	$-C(=NH)NH_2$	1	C	Single bond
334		$-CH_3$	$-C(=NH)NH_2$	1	C	Single bond
335	$-CHCH_2C(CH_3)$ with OH on the CH	$-CH_3$	$-C(=NH)NH_2$	1	C	Single bond

Table 1 (continued)

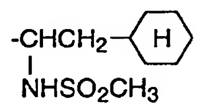
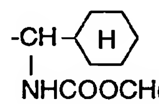
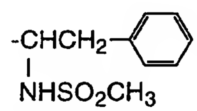
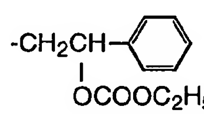
Compound No.	$-R^1\left(\begin{array}{c}-D-(CH)_m-E-R^4\\ \vert \\ R^5\end{array}\right)$	$-R^2$	$-R^3$	n	A	Broken line
336	$-CH(NHCOOC(CH_3)_3)CH_2CH(C_2H_5)_2$	$-CH_3$	$-C(=NH)NH_2$	1	C	Single bond
337	$-CH(NHSO_2CH_3)CH_2C(CH_3)_3$	$-CH_3$	$-C(=NH)NH_2$	1	C	Single bond
338		$-CH_3$	$-C(=NH)NH_2$	1	C	——
339		$-CH_3$	$-C(=NH)NH_2$	1	C	——
340		$-CH_3$	$-C(=NH)NH_2$	1	C	——
341		$-CH_3$	$-C(=NH)NH_2$	1	C	——
342	$-CH(NHCOOC(CH_3)_3)CH_2CH(C_2H_5)_2$	$-CH_3$	$-C(=NH)NH_2$	1	C	——
343	$-CH(NHSO_2CH_3)CH_2C(CH_3)_3$	$-CH_3$	$-C(=NH)NH_2$	1	C	——
344	$-CH(OH)CH_2C(CH_3)_3$	$-CH_3$	$-C(=NH)NH_2$	1	C	——

Table 1 (continued)

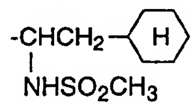
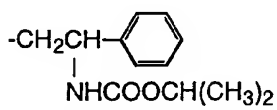
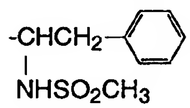
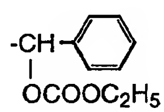
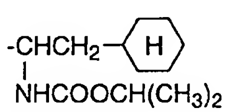
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4 \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
345		$-CH_3$	$-C(=NH)NH_2$	1	N	——
346		$-CH_3$	$-C(=NH)NH_2$	1	N	——
347		$-CH_3$	$-C(=NH)NH_2$	1	N	——
348		$-CH_3$	$-C(=NH)NH_2$	1	N	——
349	$-CH(NHSO_2CH_3)CH_2C(CH_3)_3$	$-CH_3$	$-C(=NH)NH_2$	1	N	——
350	$-CH(NHCOOC(CH_3)_3)CH_2CH(C_2H_5)_2$	$-CH_3$	$-C(=NH)NH_2$	1	N	——
351	$-CH(OH)CH_2C(CH_3)_3$	$-CH_3$	$-C(=NH)NH_2$	1	N	——
352		$-CH_3$	$-C(=NH)NH_2$	2	C	Single bond
353		$-CH_3$	$-C(=NH)NH_2$	2	C	Single bond

Table 1 (continued)

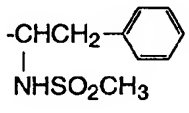
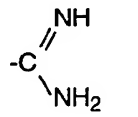
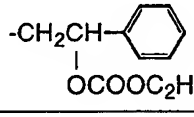
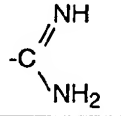
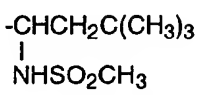
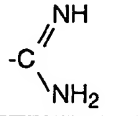
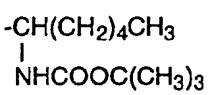
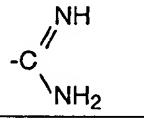
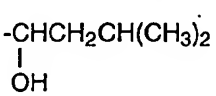
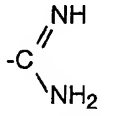
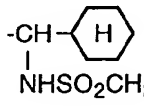
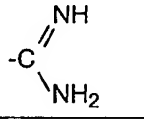
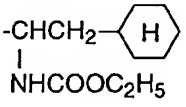
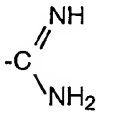
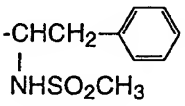
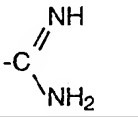
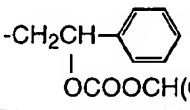
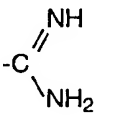
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
354		$-CH_3$		2	C	Single bond
355		$-CH_3$		2	C	Single bond
356		$-CH_3$		2	C	Single bond
357		$-CH_3$		2	C	Single bond
358		$-CH_3$		2	C	Single bond
359		$-CH_3$		2	C	——
360		$-CH_3$		2	C	——
361		$-CH_3$		2	C	——
362		$-CH_3$		2	C	——

Table 1 (continued)

Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
363	$-CHCH_2C(CH_3)_3$ $NHSO_2CH_3$	$-CH_3$	$-C(=NH)-NH_2$	2	C	——
364	$-CHC(SCH_3)(CH_3)_2$ $NHCOOC(CH_3)_3$	$-CH_3$	$-C(=NH)-NH_2$	2	C	——
365	$-CHCH_2CH(CH_3)_3$ NH_2	$-CH_3$	$-C(=NH)-NH_2$	2	C	——
366	$-CHCH_2-C_6H_4-H$ $NHCOOC_2H_5$	$-CH_3$	$-C(=NH)-NH_2$	2	N	——
367	$-CHCH_2-C_6H_4-H$ $NHSO_2CH_3$	$-CH_3$	$-C(=NH)-NH_2$	2	N	——
368	$-CH-C_6H_5$ $NHSO_2CH_3$	$-CH_3$	$-C(=NH)-NH_2$	2	N	——
369	$-CHCH_2-C_6H_4-COOH$ $OCOOCH(CH_3)_2$	$-CH_3$	$-C(=NH)-NH_2$	2	N	——
370	$-CHCH_2C(CH_3)_3$ $NHSO_2CH_2COOH$	$-CH_3$	$-C(=NH)-NH_2$	2	N	——
371	$-CH(CH_2)_2SCH_3$ $NHCOOC(CH_3)_3$	$-CH_3$	$-C(=NH)-NH_2$	2	N	——
372	$-CH_2CH(CH_2)_3CH_3$ OH	$-CH_3$	$-C(=NH)-NH_2$	2	N	——

Table 1 (continued)

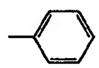
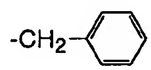
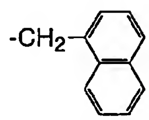
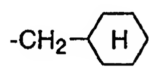
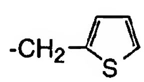
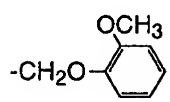
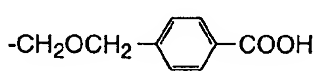
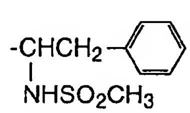
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \vert \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
373		-H	$-C(=NOH)NH_2$	1	C	Single bond
374		-H	$-C(=NOH)NH_2$	1	C	Single bond
375		-H	$-C(=NOH)NH_2$	1	C	Single bond
376		-H	$-C(=NOH)NH_2$	1	C	Single bond
377		-H	$-C(=NOH)NH_2$	1	C	Single bond
378		-H	$-C(=NOH)NH_2$	1	C	Single bond
379		-H	$-C(=NOH)NH_2$	1	C	Single bond
380	$-CH_2SC_2H_5$	-H	$-C(=NOH)NH_2$	1	C	Single bond
381	$-(CH_2)_4COOH$	-H	$-C(=NOH)NH_2$	1	C	Single bond
382		-H	$-C(=NOH)NH_2$	1	C	Single bond

Table 1 (continued)

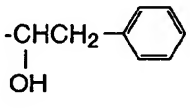
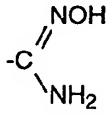
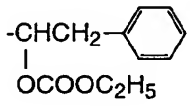
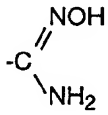
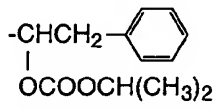
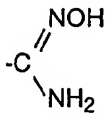
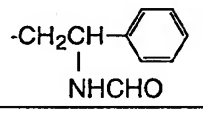
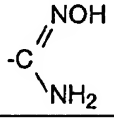
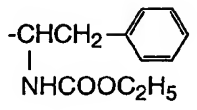
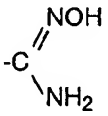
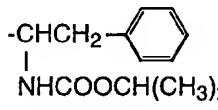
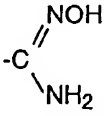
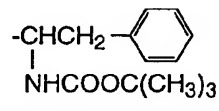
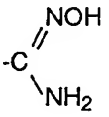
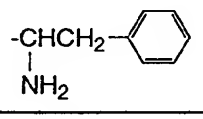
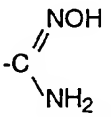
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
383		-H		1	C	Single bond
384		-H		1	C	Single bond
385		-H		1	C	Single bond
386		-H		1	C	Single bond
387		-H		1	C	Single bond
388		-H		1	C	Single bond
389		-H		1	C	Single bond
390		-H		1	C	Single bond

Table 1 (continued)

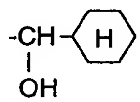
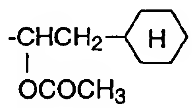
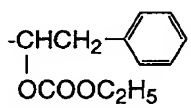
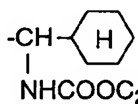
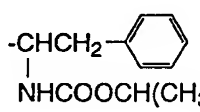
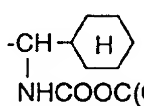
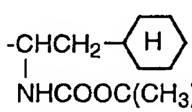
Compound No.	$-R^1\left(-D-(\underset{R^5}{CH})_m-E-R^4\right)$	$-R^2$	$-R^3$	n	A	Broken line
391		-H	$-C(=NOH)NH_2$	1	C	Single bond
392		-H	$-C(=NOH)NH_2$	1	C	Single bond
393		-H	$-C(=NOH)NH_2$	1	C	Single bond
394		-H	$-C(=NOH)NH_2$	1	C	Single bond
395		-H	$-C(=NOH)NH_2$	1	C	Single bond
396		-H	$-C(=NOH)NH_2$	1	C	Single bond
397		-H	$-C(=NOH)NH_2$	1	C	Single bond
398		-H	$-C(=NOH)NH_2$	1	C	Single bond

Table 1 (continued)

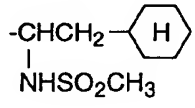
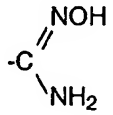
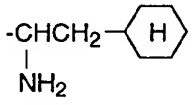
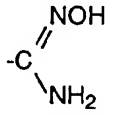
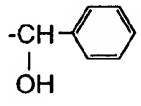
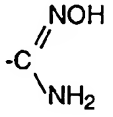
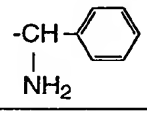
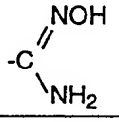
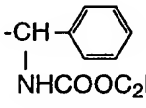
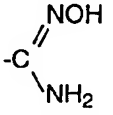
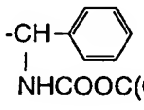
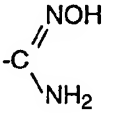
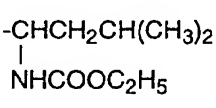
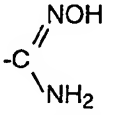
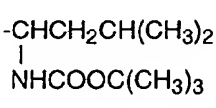
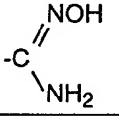
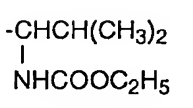
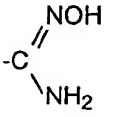
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
399		-H		1	C	Single bond
400		-H		1	C	Single bond
401		-H		1	C	Single bond
402		-H		1	C	Single bond
403		-H		1	C	Single bond
404		-H		1	C	Single bond
405		-H		1	C	Single bond
406		-H		1	C	Single bond
407		-H		1	C	Single bond

Table 1 (continued)

Compound No.	$-R^1\left(-D-(CH)_m-E-R^4 \atop R^5\right)$	$-R^2$	$-R^3$	n	A	Broken line
408	$-CHCH(CH_3)_2$ $NHCOOC(CH_3)_3$	-H	$-C(=NOH)NH_2$	1	C	Single bond
409	$-CHC(CH_3)_3$ $NHCOOC_2H_5$	-H	$-C(=NOH)NH_2$	1	C	Single bond
410	$-CHC(CH_3)_3$ $NHCOOC(CH_3)_3$	-H	$-C(=NOH)NH_2$	1	C	Single bond
411	$-CH(CH_2)_4CH_3$ $NHCOOC_2H_5$	-H	$-C(=NOH)NH_2$	1	C	Single bond
412	$-CH(CH_2)_4CH_3$ $NHCOOC(CH_3)_3$	-H	$-C(=NOH)NH_2$	1	C	Single bond
413	$-CHCH_2CH_2SCH_3$ $NHCOOC_2H_5$	-H	$-C(=NOH)NH_2$	1	C	Single bond
414	$-CHCH_2CH_2SCH_3$ $NHCOOC(CH_3)_3$	-H	$-C(=NOH)NH_2$	1	C	Single bond
415	$-CH(CH_2)_4CH_3$ $OCOOC_2H_5$	-H	$-C(=NOH)NH_2$	1	C	Single bond
416	$-CHCH_2C(CH_3)_3$ $OCOOC_2H_5$	-H	$-C(=NOH)NH_2$	1	C	Single bond
417	$-CHCH_2CH(C_2H_5)_2$ $NHCOOC_2H_5$	-H	$-C(=NOH)NH_2$	1	C	Single bond
418	$-CHCH_2C(CH_3)_3$ $NHCOOC_2H_5$	-H	$-C(=NOH)NH_2$	1	C	Single bond

Table 1 (continued)

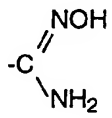
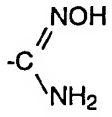
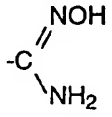
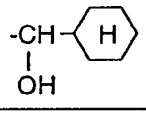
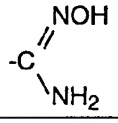
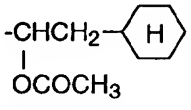
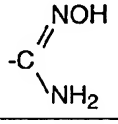
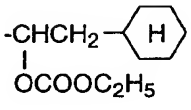
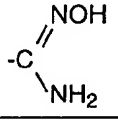
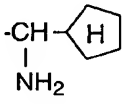
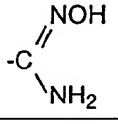
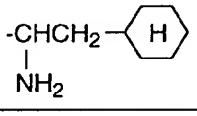
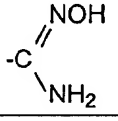
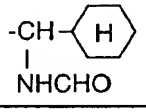
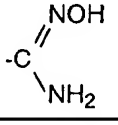
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
419	$-CHC(SCH_3)(CH_3)_2$ $NHCOOC_2H_5$	-H		1	C	Single bond
420	$-CHCH_2C(CH_3)_3$ $NHCOOCH(CH_3)_2$	-H		1	C	Single bond
421	$-CHCH_2C(CH_3)_3$ NH_2	-H		1	C	Single bond
422		-H		1	C	——
423		-H		1	C	——
424		-H		1	C	——
425		-H		1	C	——
426		-H		1	C	——
427		-H		1	C	——

Table 1 (continued)

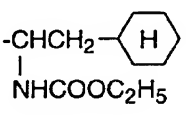
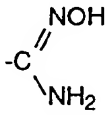
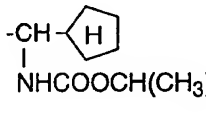
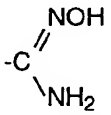
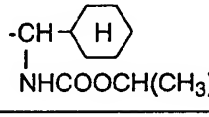
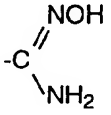
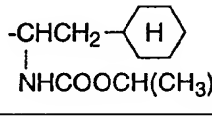
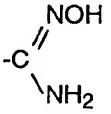
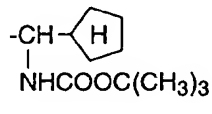
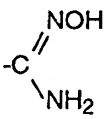
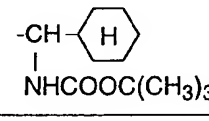
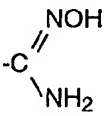
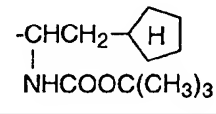
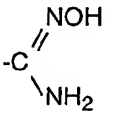
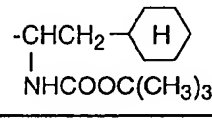
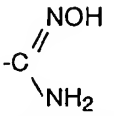
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
428		-H		1	C	——
429		-H		1	C	——
430		-H		1	C	——
431		-H		1	C	——
432		-H		1	C	——
433		-H		1	C	——
434		-H		1	C	——
435		-H		1	C	——

Table 1 (continued)

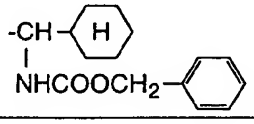
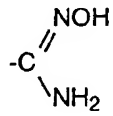
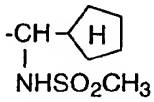
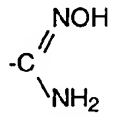
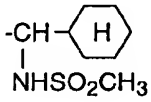
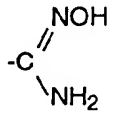
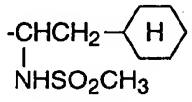
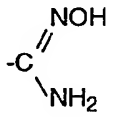
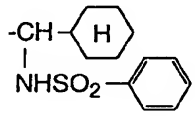
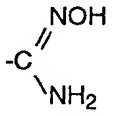
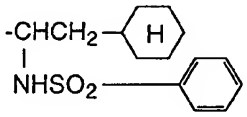
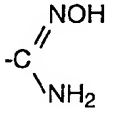
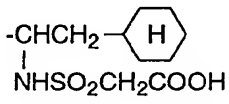
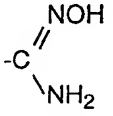
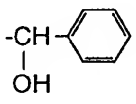
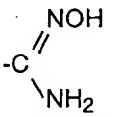
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
436		-H		1	C	——
437		-H		1	C	——
438		-H		1	C	——
439		-H		1	C	——
440		-H		1	C	——
441		-H		1	C	——
442		-H		1	C	——
443		-H		1	C	——

Table 1 (continued)

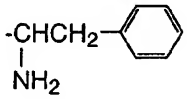
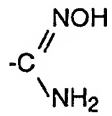
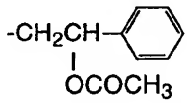
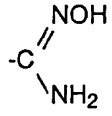
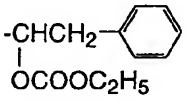
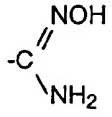
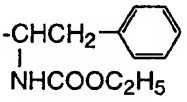
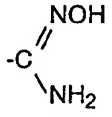
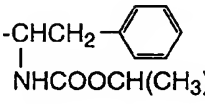
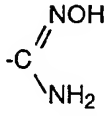
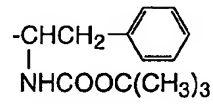
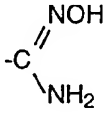
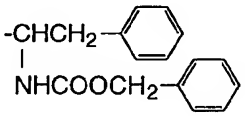
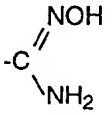
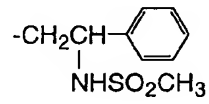
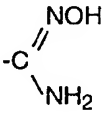
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
444		-H		1	C	——
445		-H		1	C	——
446		-H		1	C	——
447		-H		1	C	——
448		-H		1	C	——
449		-H		1	C	——
450		-H		1	C	——
451		-H		1	C	——

Table 1 (continued)

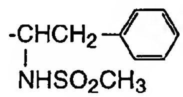
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \vert \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
452		H	$-C(=NOH)NH_2$	1	C	——
453	$-CH(CH_2)_4CH_3$ with OH on CH	-H	$-C(=NOH)NH_2$	1	C	——
454	$-CHCH_2C(CH_3)_3$ with OH on CH	H	$-C(=NOH)NH_2$	1	C	——
455	$-CHCH_2CH(C_2H_5)_2$ with $OCOCH_3$ on CH	-H	$-C(=NOH)NH_2$	1	C	——
456	$-CHCH_2C(CH_3)_3$ with $OCOOC_2H_5$ on CH	-H	$-C(=NOH)NH_2$	1	C	——
457	$-CH_2CH(CH_2)_2CH_3$ with NHCHO on CH	H	$-C(=NOH)NH_2$	1	C	——
458	$-CHCH_2C(CH_3)_3$ with $NHCOOCH_3$ on CH	-H	$-C(=NOH)NH_2$	1	C	——
459	$-CH(CH_2)_4CH_3$ with $NHCOOC_2H_5$ on CH	-H	$-C(=NOH)NH_2$	1	C	——
460	$-CHCH_2CH(C_2H_5)_2$ with $NHCOOC_2H_5$ on CH	-H	$-C(=NOH)NH_2$	1	C	——
461	$-CHCH_2C(CH_3)_3$ with $NHCOOC_2H_5$ on CH	-H	$-C(=NOH)NH_2$	1	C	——

Table 1 (continued)

Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
462	$-CH(CH_2)_4CH_3$ $NHCOOCH(CH_3)_2$	-H	$-C(=NOH)-NH_2$	1	C	——
463	$-CHCH_2CH(C_2H_5)_2$ $NHCOOCH(CH_3)_2$	-H	$-C(=NOH)-NH_2$	1	C	——
464	$-CHCH_2C(CH_3)_3$ $NHCOOCH(CH_3)_2$	-H	$-C(=NOH)-NH_2$	1	C	——
465	$-CH(CH_2)_4CH_3$ $NHCOOC(CH_3)_3$	-H	$-C(=NOH)-NH_2$	1	C	——
466	$-CHCH_2CH(C_2H_5)_2$ $NHCOOC(CH_3)_3$	-H	$-C(=NOH)-NH_2$	1	C	——
467	$-CHCH_2C(CH_3)_3$ $NHCOOC(CH_3)_3$	-H	$-C(=NOH)-NH_2$	1	C	——
468	$-CH(CH_2)_2SCH_3$ $NHCOOC(CH_3)_3$	-H	$-C(=NOH)-NH_2$	1	C	——
469	$-CHCH_2C(CH_3)_3$ $NHCOOCH_2-C_6H_5$	-H	$-C(=NOH)-NH_2$	1	C	——
470	$-CHCH_2C(CH_3)_3$ NH_2	-H	$-C(=NOH)-NH_2$	1	C	——
471	$-CH-C_6H_5$ $NHCOOC_2H_5$	-H	$-C(=NOH)-NH_2$	1	C	——

Table 1 (continued)

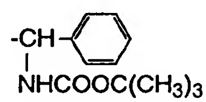
Compound No.	$-R^1$ ($-D-(CH)_m-E-R^4$, with R^5 on CH)	$-R^2$	$-R^3$	n	A	Broken line
472		-H	$-C(=NOH)NH_2$	1	C	——
473	$-CH(NHCOOC_2H_5)CH_2CH(CH_3)_2$	-H	$-C(=NOH)NH_2$	1	C	——
474	$-CH(NHCOOC(CH_3)_3)CH_2CH(CH_3)_2$	-H	$-C(=NOH)NH_2$	1	C	——
475	$-CH(NHCOOCH(CH_3)_2)(CH_2)_2CH_3$	H	$-C(=NOH)NH_2$	1	C	——
476	$-CH(NHCOOC(CH_3)_3)(CH_2)_2CH_3$	-H	$-C(=NOH)NH_2$	1	C	——
477	$-CH(NHCOOCH(CH_3)_2)CH(CH_3)_2$	H	$-C(=NOH)NH_2$	1	C	——
478	$-CH(NHCOOC(CH_3)_3)CH(CH_3)_2$	-H	$-C(=NOH)NH_2$	1	C	——
479	$-CH(NHCOOCH(CH_3)_2)C(CH_3)_3$	-H	$-C(=NOH)NH_2$	1	C	——
480	$-CH(NHCOOC(CH_3)_3)C(CH_3)_3$	-H	$-C(=NOH)NH_2$	1	C	——
481	$-CH(NHCOOC_2H_5)CH_2Si(CH_3)_3$	-H	$-C(=NOH)NH_2$	1	C	——

Table 1 (continued)

Compound No.	$-R^1\left(-D-(\underset{R^5}{CH})_m-E-R^4\right)$	$-R^2$	$-R^3$	n	A	Broken line
482	$-\underset{NHCOOCH(CH_3)_2}{CH}CH_2Si(CH_3)_3$	-H	$-C(=NOH)NH_2$	1	C	——
483	$-\underset{NHCOOC_2H_5}{CH}CH_2CH_2SCH_3$	H	$-C(=NOH)NH_2$	1	C	——
484	$-\underset{NHCOOCH(CH_3)_2}{CH}CH_2CH_2SCH_3$	-H	$-C(=NOH)NH_2$	1	C	——
485	$-\underset{NHCOOC_2H_5}{CH}CH_2OC(CH_3)_3$	-H	$-C(=NOH)NH_2$	1	C	——
486	$-\underset{NHCOOCH(CH_3)_2}{CH}CH_2OC(CH_3)_3$	-H	$-C(=NOH)NH_2$	1	C	——
487	$-\underset{NHCOOC_2H_5}{CH}CH_2OC(CH_3)_2C_2H_5$	-H	$-C(=NOH)NH_2$	1	C	——
488	$-\underset{NHCOOCH(CH_3)_2}{CH}CH_2OC(CH_3)_2C_2H_5$	-H	$-C(=NOH)NH_2$	1	C	——
489	$-\underset{NHCOOC_2H_5}{CH}CH_2OC(C_2H_5)_2CH_3$	-H	$-C(=NOH)NH_2$	1	C	——
490	$-\underset{NHCOOCH(CH_3)_2}{CH}CH_2OC(C_2H_5)_2CH_3$	-H	$-C(=NOH)NH_2$	1	C	——
491	$-\underset{NHCOOCH(CH_3)_2}{CH}CH_2OC(CH_3)_2CH(CH_3)_2$	-H	$-C(=NOH)NH_2$	1	C	——
492	$-\underset{NHCOOC_2H_5}{CH}CH_2SC(CH_3)_3$	-H	$-C(=NOH)NH_2$	1	C	——

Table 1 (continued)

Compound No.	$-R^1\left(\begin{array}{c}-D-(CH)_m-E-R^4\\ \vert \\ R^5\end{array}\right)$	$-R^2$	$-R^3$	n	A	Broken line
493	$-CHCH_2SC(CH_3)_2C_2H_5$ $NHCOOC_2H_5$	-H	$-C(=NOH)NH_2$	1	C	——
494	$-CHCH_2SC(CH_3)_2C_2H_5$ $NHCOOCH(CH_3)_2$	-H	$-C(=NOH)NH_2$	1	C	——
495	$-CHC(CH_3)_2SC_2H_5$ $NHCOOC_2H_5$	-H	$-C(=NOH)NH_2$	1	C	——
496	$-CHC(CH_3)_2SC_2H_5$ $NHCOOCH(CH_3)_2$	-H	$-C(=NOH)NH_2$	1	C	——
497	$-CHC(CH_3)_2SCH(CH_3)_2$ $NHCOOC_2H_5$	-H	$-C(=NOH)NH_2$	1	C	——
498	$-CHC(CH_3)_2SCH(CH_3)_2$ $NHCOOCH(CH_3)_2$	H	$-C(=NOH)NH_2$	1	C	——
499	$-CHC(CH_3)_2SCH(C_2H_5)_2$ $NHCOOC_2H_5$	-H	$-C(=NOH)NH_2$	1	C	——
500	$-CHC(CH_3)_2SCH(C_2H_5)_2$ $NHCOOCH(CH_3)_2$	-H	$-C(=NOH)NH_2$	1	C	——
501	$-CH(CH_2)_4CH_3$ $NHSO_2CH_3$	H	$-C(=NOH)NH_2$	1	C	——
502	$-CHCH_2C(CH_3)_3$ $NHSO_2CH_3$	-H	$-C(=NOH)NH_2$	1	C	——

Table 1 (continued)

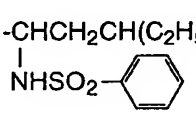
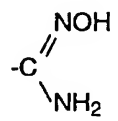
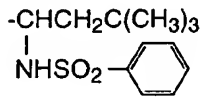
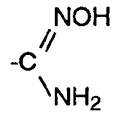
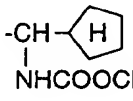
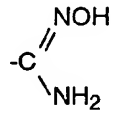
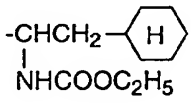
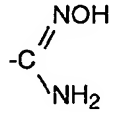
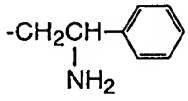
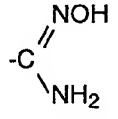
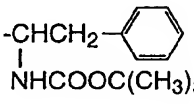
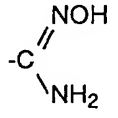
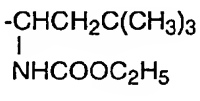
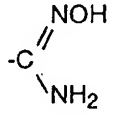
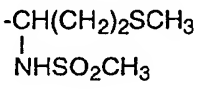
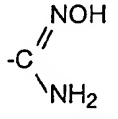
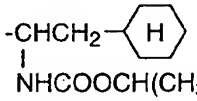
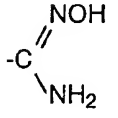
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
503		H		1	C	——
504		-H		1	C	——
505		-H		1	N	——
506		H		1	N	——
507		-H		1	N	——
508		-H		1	N	——
509		-H		1	N	——
510		-H		1	N	——
511		$-CH_3$		2	C	Single bond

Table 1 (continued)

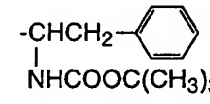
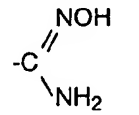
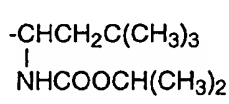
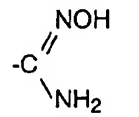
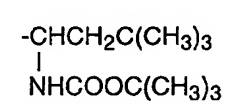
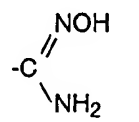
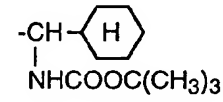
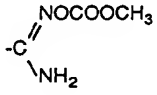
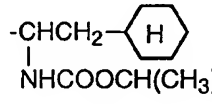
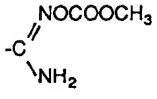
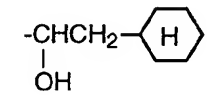
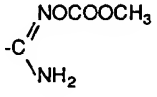
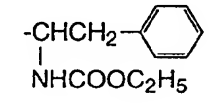
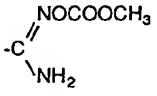
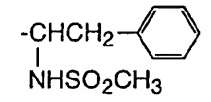
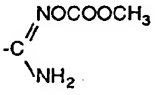
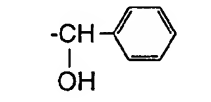
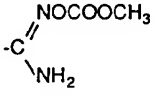
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
512		$-CH_3$		2	C	Single bond
513		$-CH_3$		2	C	Single bond
514		$-CH_3$		2	C	Single bond
515		-H		1	C	Single bond
516		-H		1	C	Single bond
517		-H		1	C	Single bond
518		-H		1	C	Single bond
519		-H		1	C	Single bond
520		-H		1	C	Single bond

Table 1 (continued)

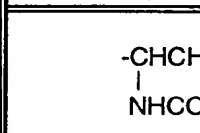
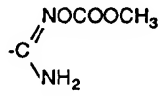
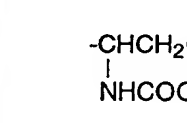
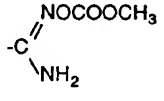
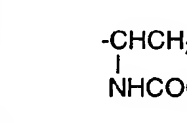
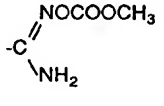
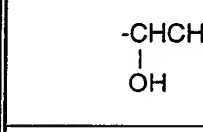
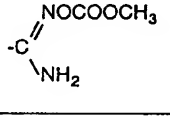
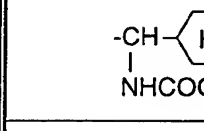
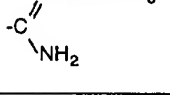
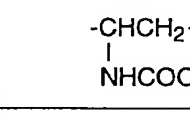
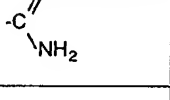
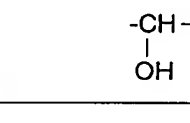
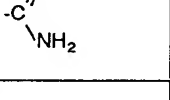
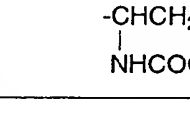
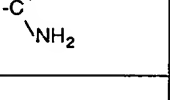
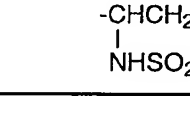
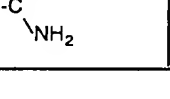
Compound No.	$-R^1\left(-D-(CH)_m-E-R^4 \atop R^5\right)$	$-R^2$	$-R^3$	n	A	Broken line
521		-H		1	C	Single bond
522		-H		1	C	Single bond
523		-H		1	C	Single bond
524		-H		1	C	Single bond
525		-H		1	C	——
526		-H		1	C	——
527		-H		1	C	——
528		-H		1	C	——
529		-H		1	C	——

Table 1 (continued)

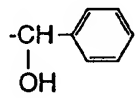
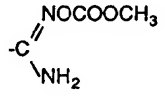
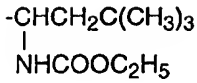
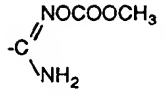
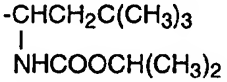
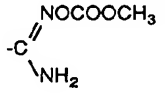
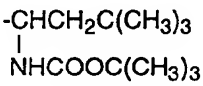
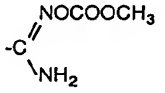
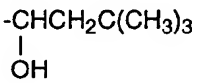
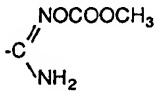
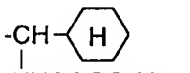
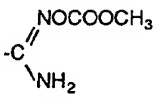
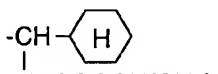
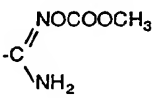
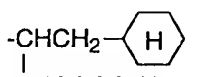
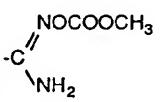
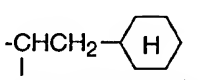
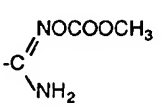
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
530		-H		1	C	——
531		-H		1	C	——
532		-H		1	C	——
533		-H		1	C	——
534		-H		1	C	——
535		-H		1	C	——
536		-H		1	C	——
537		-H		1	C	——
538		-H		1	C	——

Table 1 (continued)

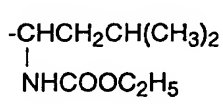
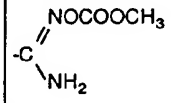
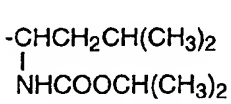
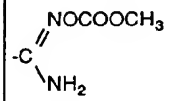
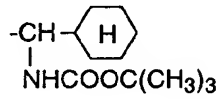
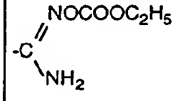
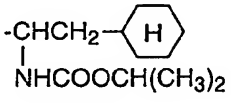
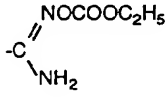
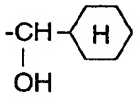
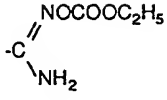
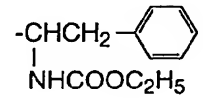
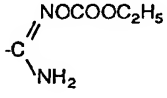
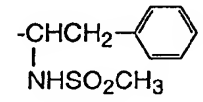
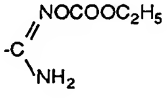
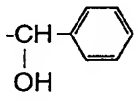
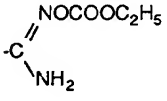
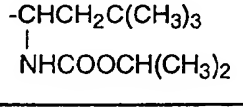
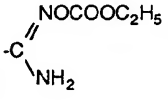
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
539		-H		1	C	——
540		-H		1	C	——
541		-H		1	C	Single bond
542		-H		1	C	Single bond
543		-H		1	C	Single bond
544		-H		1	C	Single bond
545		-H		1	C	Single bond
546		-H		1	C	Single bond
547		-H		1	C	Single bond

Table 1 (continued)

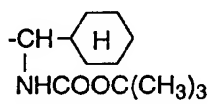
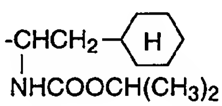
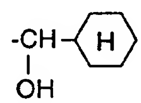
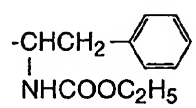
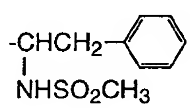
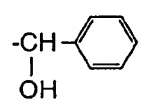
Compound No.	$-R^1\left(\begin{array}{c}-D-(CH)_m-E-R^4 \\ \vert \\ R^5\end{array}\right)$	$-R^2$	$-R^3$	n	A	Broken line
548	$-CH(OH)CH_2C(CH_3)_3$	-H	$-C(=NOCOOC_2H_5)NH_2$	1	C	Single bond
549		-H	$-C(=NOCOOC_2H_5)NH_2$	1	C	——
550		-H	$-C(=NOCOOC_2H_5)NH_2$	1	C	——
551		-H	$-C(=NOCOOC_2H_5)NH_2$	1	C	——
552		-H	$-C(=NOCOOC_2H_5)NH_2$	1	C	——
553		-H	$-C(=NOCOOC_2H_5)NH_2$	1	C	——
554		-H	$-C(=NOCOOC_2H_5)NH_2$	1	C	——
555	$-CH(NHCOOCH(CH_3)_2)CH_2C(CH_3)_3$	-H	$-C(=NOCOOC_2H_5)NH_2$	1	C	——
556	$-CH(OH)CH_2C(CH_3)_3$	-H	$-C(=NOCOOC_2H_5)NH_2$	1	C	——

Table 1 (continued)

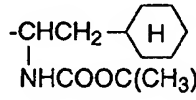
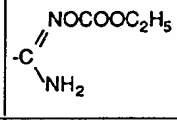
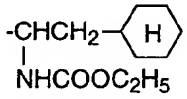
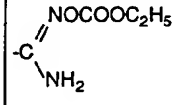
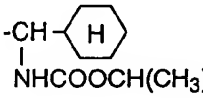
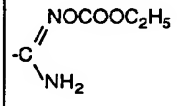
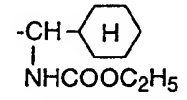
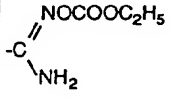
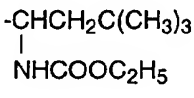
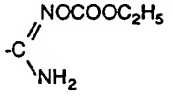
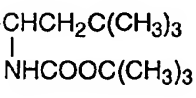
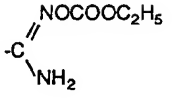
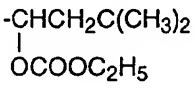
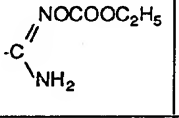
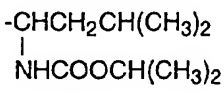
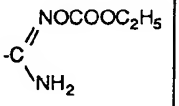
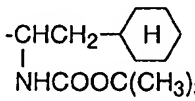
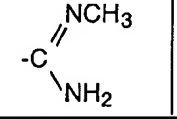
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
557		-H		1	C	——
558		-H		1	C	——
559		-H		1	C	——
560		-H		1	C	——
561		-H		1	C	——
562		-H		1	C	——
563		-H		1	C	——
564		-H		1	C	——
565		-H		1	C	Single bond

Table 1 (continued)

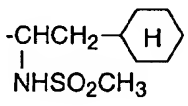
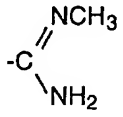
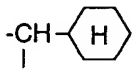
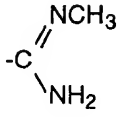
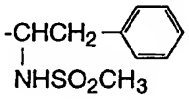
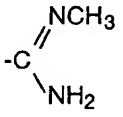
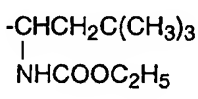
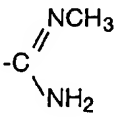
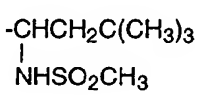
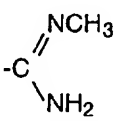
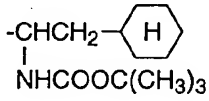
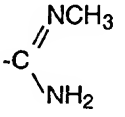
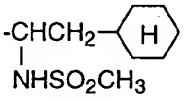
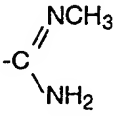
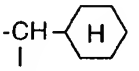
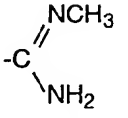
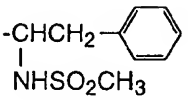
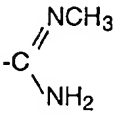
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
566		-H		1	C	Single bond
567		-H		1	C	Single bond
568		-H		1	C	Single bond
569		-H		1	C	Single bond
570		-H		1	C	Single bond
571		-H		1	C	——
572		-H		1	C	——
573		-H		1	C	——
574		-H		1	C	——

Table 1 (continued)

Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
575	$-CHCH_2C(CH_3)_3$ $NHCOOC_2H_5$	-H	$-C(=NCH_3)-NH_2$	1	C	——
576	$-CHCH_2C(CH_3)_3$ $NHSO_2CH_3$	-H	$-C(=NCH_3)-NH_2$	1	C	——
577	$-CHCH_2$-(H) $NHCOOC(CH_3)_3$	-H	$-C(=NCOCH_3)-NH_2$	1	C	Single bond
578	$-CHCH_2$-(H) $NHSO_2CH_3$	-H	$-C(=NCOCH_3)-NH_2$	1	C	Single bond
579	$-CH$-(H) OH	-H	$-C(=NCOCH_3)-NH_2$	1	C	Single bond
580	$-CHCH_2$-(benzene) $NHSO_2CH_3$	-H	$-C(=NCOCH_3)-NH_2$	1	C	Single bond
581	$-CHCH_2C(CH_3)_3$ $NHCOOC_2H_5$	-H	$-C(=NCOCH_3)-NH_2$	1	C	Single bond
582	$-CHCH_2C(CH_3)_3$ $NHSO_2CH_3$	-H	$-C(=NCOCH_3)-NH_2$	1	C	Single bond
583	$-CHCH_2$-(H) $NHCOOC(CH_3)_3$	-H	$-C(=NCOCH_3)-NH_2$	1	C	——

Table 1 (continued)

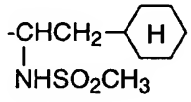
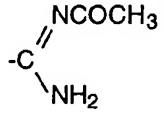
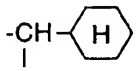
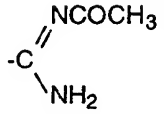
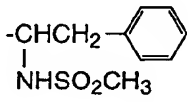
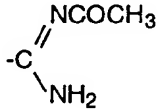
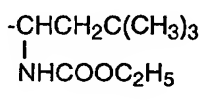
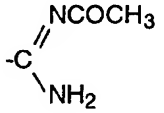
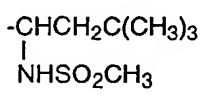
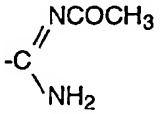
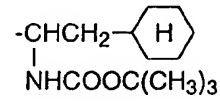
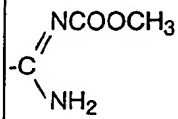
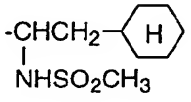
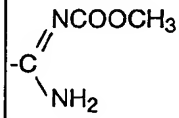
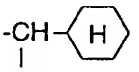
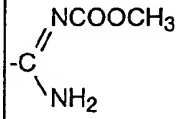
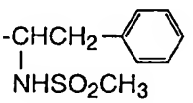
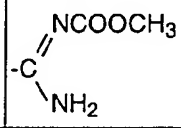
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
584		-H		1	C	——
585		-H		1	C	——
586		-H		1	C	——
587		-H		1	C	——
588		-H		1	C	——
589		-H		1	C	Single bond
590		-H		1	C	Single bond
591		-H		1	C	Single bond
592		-H		1	C	Single bond

Table 1 (continued)

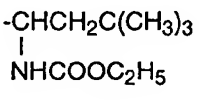
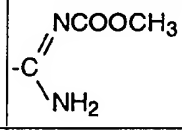
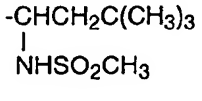
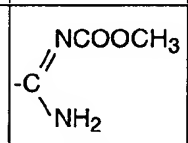
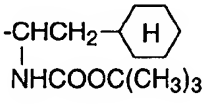
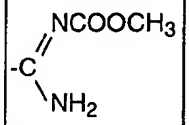
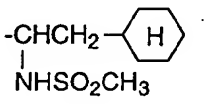
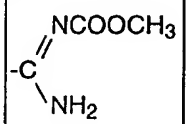
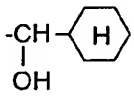
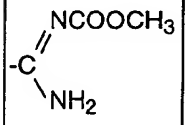
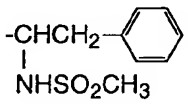
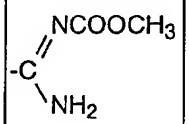
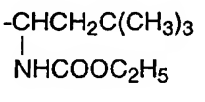
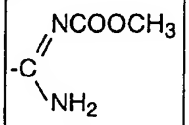
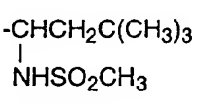
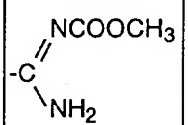
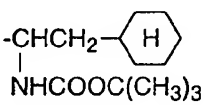
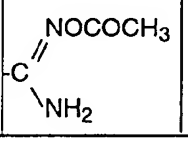
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
593		-H		1	C	Single bond
594		-H		1	C	Single bond
595		-H		1	C	——
596		-H		1	C	——
597		-H		1	C	——
598		-H		1	C	——
599		-H		1	C	——
600		-H		1	C	——
601		-H		1	C	Single bond

Table 1 (continued)

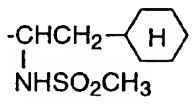
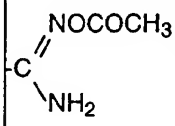
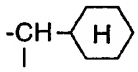
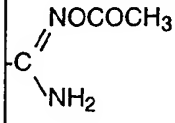
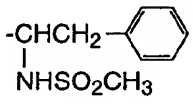
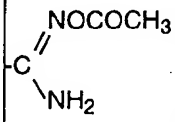
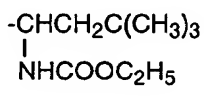
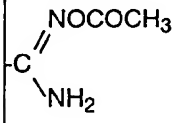
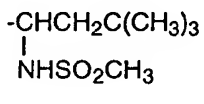
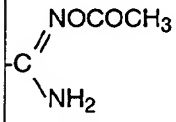
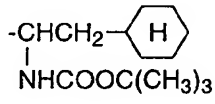
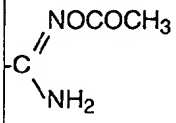
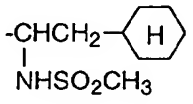
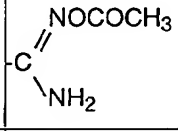
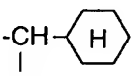
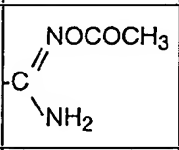
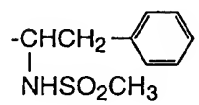
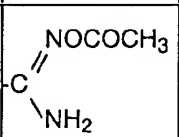
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
602		-H		1	C	Single bond
603		-H		1	C	Single bond
604		-H		1	C	Single bond
605		-H		1	C	Single bond
606		-H		1	C	Single bond
607		-H		1	C	——
608		-H		1	C	——
609		-H		1	C	——
610		-H		1	C	——

Table 1 (continued)

Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
611	$-CHCH_2C(CH_3)_3$ $NHCOOC_2H_5$	-H	$-C(=NOCOCH_3)-NH_2$	1	C	——
612	$-CHCH_2C(CH_3)_3$ $NHSO_2CH_3$	-H	$-C(=NOCOCH_3)-NH_2$	1	C	——
613	$-CHCH_2-C_6H_4-H$ $NHCOOC(CH_3)_3$	-H	$-C(=NOCH_3)-NH_2$	1	C	Single bond
614	$-CHCH_2-C_6H_4-H$ $NHSO_2CH_3$	-H	$-C(=NOCH_3)-NH_2$	1	C	Single bond
615	$-CH(OH)-C_6H_4-H$	-H	$-C(=NOCH_3)-NH_2$	1	C	Single bond
616	$-CHCH_2-C_6H_5$ $NHSO_2CH_3$	-H	$-C(=NOCH_3)-NH_2$	1	C	Single bond
617	$-CHCH_2C(CH_3)_3$ $NHCOOC_2H_5$	-H	$-C(=NOCH_3)-NH_2$	1	C	Single bond
618	$-CHCH_2C(CH_3)_3$ $NHSO_2CH_3$	-H	$-C(=NOCH_3)-NH_2$	1	C	Single bond
619	$-CHCH_2-C_6H_4-H$ $NHCOOC(CH_3)_3$	-H	$-C(=NOCH_3)-NH_2$	1	C	——

Table 1 (continued)

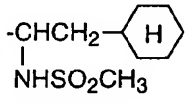
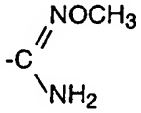
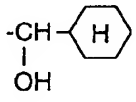
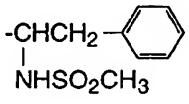
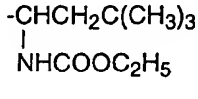
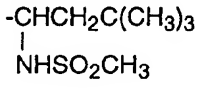
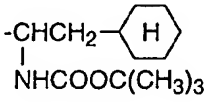
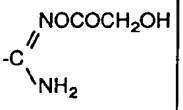
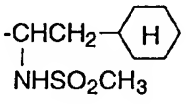
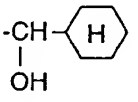
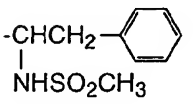
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
620		-H		1	C	——
621		-H		1	C	——
622		-H		1	C	——
623		-H		1	C	——
624		-H		1	C	——
625		-H		1	C	Single bond
626		-H		1	C	Single bond
627		-H		1	C	Single bond
628		-H		1	C	Single bond

Table 1 (continued)

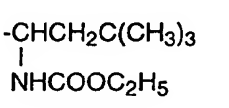
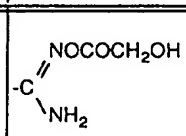
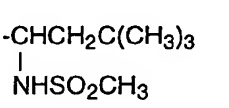
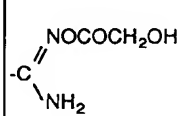
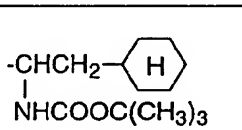
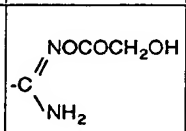
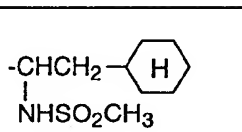
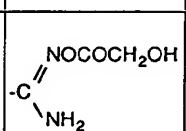
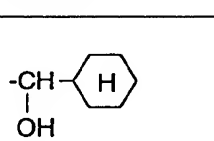
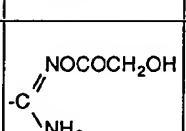
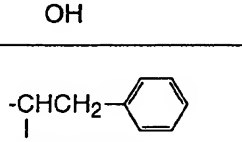
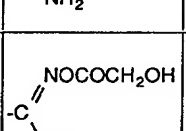
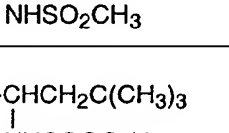
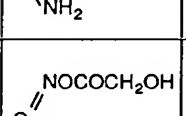
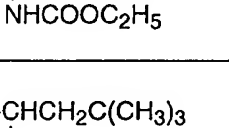
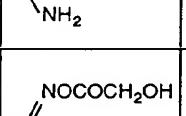
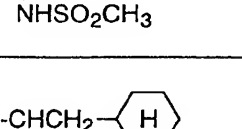
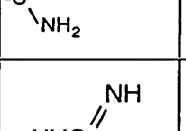
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
629		-H		1	C	Single bond
630		-H		1	C	Single bond
631		-H		1	C	——
632		-H		1	C	——
633		-H		1	C	——
634		-H		1	C	——
635		-H		1	C	——
636		-H		1	C	——
637		-H		1	C	Single bond

Table 1 (continued)

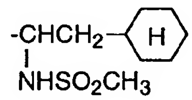
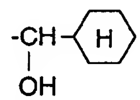
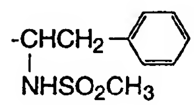
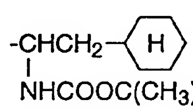
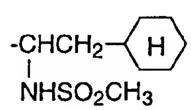
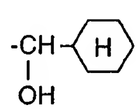
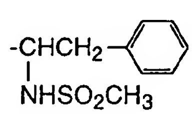
Compound No.	$-R^1\left(-D-\underset{R^5}{(CH)_m}-E-R^4\right)$	$-R^2$	$-R^3$	n	A	Broken line
638		-H	$-NHC(=NH)NH_2$	1	C	Single bond
639		-H	$-NHC(=NH)NH_2$	1	C	Single bond
640		-H	$-NHC(=NH)NH_2$	1	C	Single bond
641	$-CH(NHCOOC_2H_5)CH_2C(CH_3)_3$	-H	$-NHC(=NH)NH_2$	1	C	Single bond
642	$-CH(NHSO_2CH_3)CH_2C(CH_3)_3$	-H	$-NHC(=NH)NH_2$	1	C	Single bond
643		-H	$-NHC(=NH)NH_2$	1	C	——
644		-H	$-NHC(=NH)NH_2$	1	C	——
645		-H	$-NHC(=NH)NH_2$	1	C	——
646		-H	$-NHC(=NH)NH_2$	1	C	——

Table 1 (continued)

Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
647	$-CHCH_2C(CH_3)_3$ $NHCOOC_2H_5$	-H	$-NHC(=NH)NH_2$	1	C	——
648	$-CHCH_2C(CH_3)_3$ $NHSO_2CH_3$	-H	$-NHC(=NH)NH_2$	1	C	——
649	$-CHCH_2$-(H) $NHCOOC(CH_3)_3$	-H	$-NHC(=NCH_3)NH_2$	1	C	Single bond
650	$-CHCH_2$-(H) $NHSO_2CH_3$	-H	$-NHC(=NCH_3)NH_2$	1	C	Single bond
651	$-CH$-(H) OH	-H	$-NHC(=NCH_3)NH_2$	1	C	Single bond
652	$-CHCH_2$-(benzene) $NHSO_2CH_3$	-H	$-NHC(=NCH_3)NH_2$	1	C	Single bond
653	$-CHCH_2C(CH_3)_3$ $NHCOOC_2H_5$	-H	$-NHC(=NCH_3)NH_2$	1	C	Single bond
654	$-CHCH_2C(CH_3)_3$ $NHSO_2CH_3$	-H	$-NHC(=NCH_3)NH_2$	1	C	Single bond
655	$-CHCH_2$-(H) $NHCOOC(CH_3)_3$	-H	$-NHC(=NCH_3)NH_2$	1	C	——

Table 1 (continued)

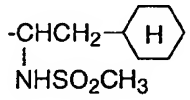
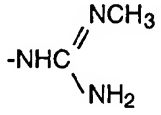
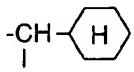
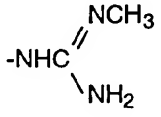
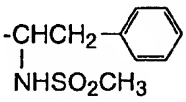
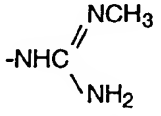
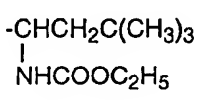
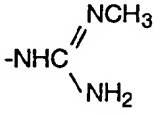
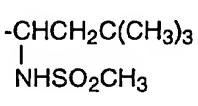
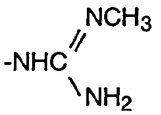
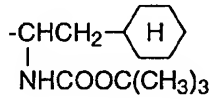
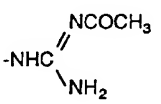
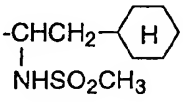
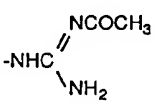
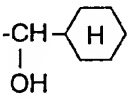
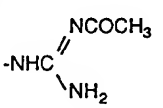
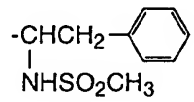
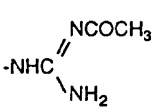
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
656		-H		1	C	——
657		-H		1	C	——
658		-H		1	C	——
659		-H		1	C	——
660		-H		1	C	——
661		-H		1	C	Single bond
662		-H		1	C	Single bond
663		-H		1	C	Single bond
664		-H		1	C	Single bond

Table 1 (continued)

Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
665	$-CHCH_2C(CH_3)_3$ $NHCOOC_2H_5$	-H	$-NHC(=NCOCH_3)NH_2$	1	C	Single bond
666	$-CHCH_2C(CH_3)_3$ $NHSO_2CH_3$	-H	$-NHC(=NCOCH_3)NH_2$	1	C	Single bond
667	$-CHCH_2-C_6H_4-H$ $NHCOOC(CH_3)_3$	-H	$-NHC(=NCOCH_3)NH_2$	1	C	——
668	$-CHCH_2-C_6H_4-H$ $NHSO_2CH_3$	-H	$-NHC(=NCOCH_3)NH_2$	1	C	——
669	$-CH(OH)-C_6H_4-H$	-H	$-NHC(=NCOCH_3)NH_2$	1	C	——
670	$-CHCH_2-C_6H_5$ $NHSO_2CH_3$	-H	$-NHC(=NCOCH_3)NH_2$	1	C	——
671	$-CHCH_2C(CH_3)_3$ $NHCOOC_2H_5$	-H	$-NHC(=NCOCH_3)NH_2$	1	C	——
672	$-CHCH_2C(CH_3)_3$ $NHSO_2CH_3$	-H	$-NHC(=NCOCH_3)NH_2$	1	C	——
673	$-CHCH_2-C_6H_4-H$ $NHCOOC(CH_3)_3$	-H	$-NHC(=NOCOCH_3)NH_2$	1	C	Single bond

Table 1 (continued)

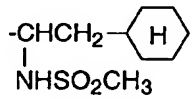
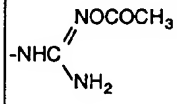
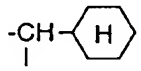
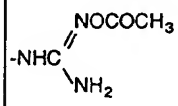
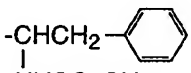
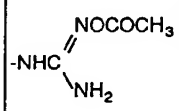
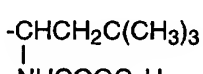
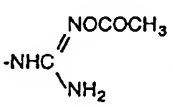
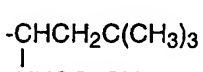
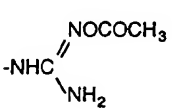
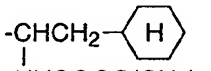
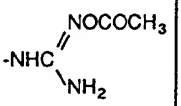
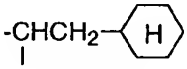
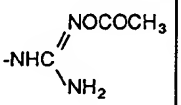
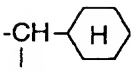
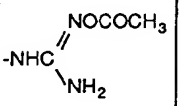
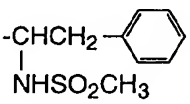
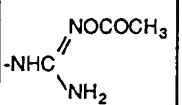
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
674		-H		1	C	Single bond
675		-H		1	C	Single bond
676		-H		1	C	Single bond
677		-H		1	C	Single bond
678		-H		1	C	Single bond
679		-H		1	C	——
680		-H		1	C	——
681		-H		1	C	——
682		-H		1	C	——

Table 1 (continued)

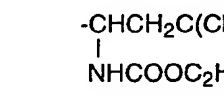
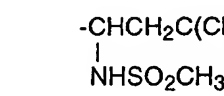
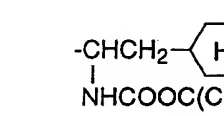
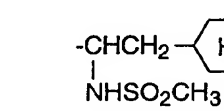
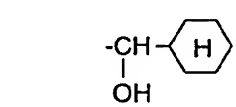
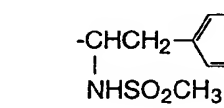
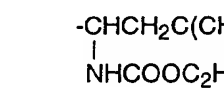
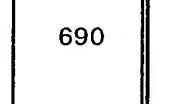
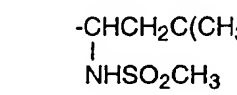
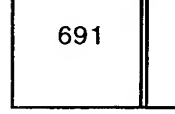
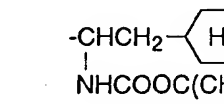
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
683		-H		1	C	——
684		-H		1	C	——
685		-H		1	C	Single bond
686		-H		1	C	Single bond
687		-H		1	C	Single bond
688		-H		1	C	Single bond
689		-H		1	C	Single bond
690		-H		1	C	Single bond
691		-H		1	C	——

Table 1 (continued)

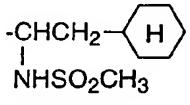
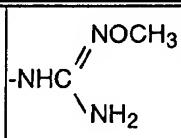
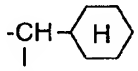
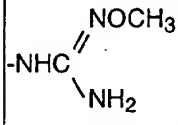
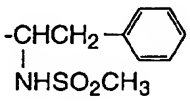
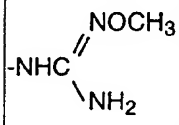
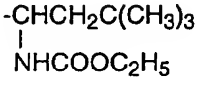
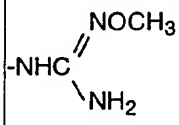
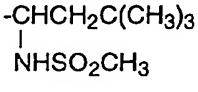
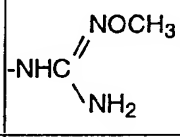
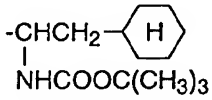
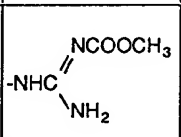
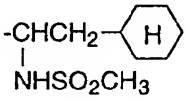
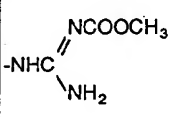
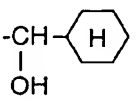
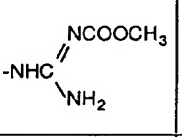
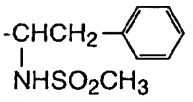
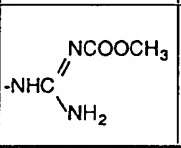
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
692		-H		1	C	——
693		-H		1	C	——
694		-H		1	C	——
695		-H		1	C	——
696		-H		1	C	——
697		-H		1	C	Single bond
698		-H		1	C	Single bond
699		-H		1	C	Single bond
700		-H		1	C	Single bond

Table 1 (continued)

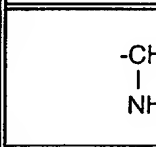
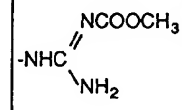
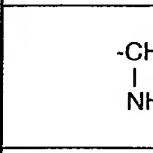
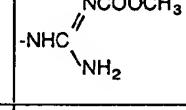
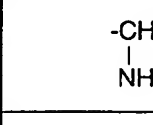
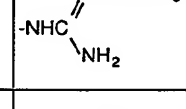
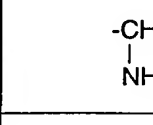
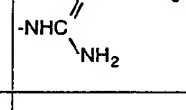
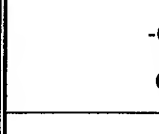
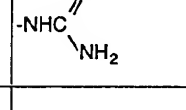
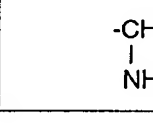
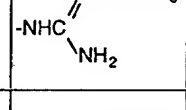
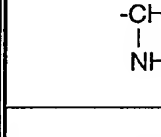
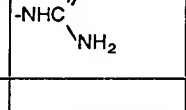
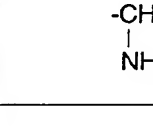
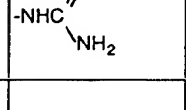
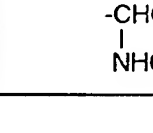
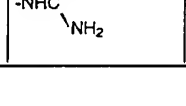
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
701		-H		1	C	Single bond
702		-H		1	C	Single bond
703		-H		1	C	——
704		-H		1	C	——
705		-H		1	C	——
706		-H		1	C	——
707		-H		1	C	——
708		-H		1	C	——
709		-H		1	C	Single bond

Table 1 (continued)

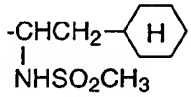
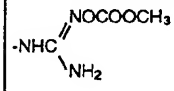
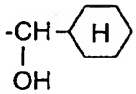
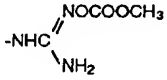
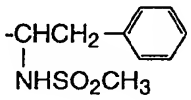
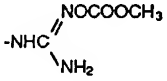
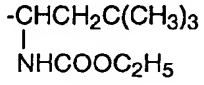
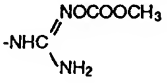
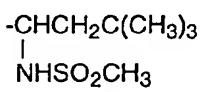
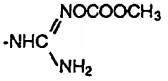
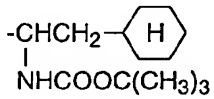
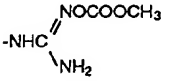
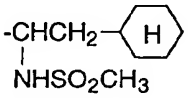
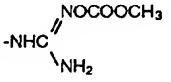
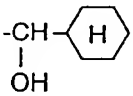
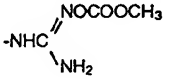
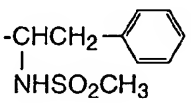
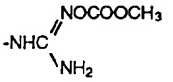
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
710		-H		1	C	Single bond
711		-H		1	C	Single bond
712		-H		1	C	Single bond
713		-H		1	C	Single bond
714		-H		1	C	Single bond
715		-H		1	C	——
716		-H		1	C	——
717		-H		1	C	——
718		-H		1	C	——

Table 1 (continued)

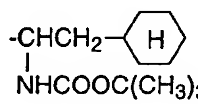
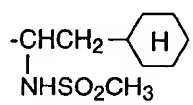
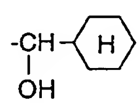
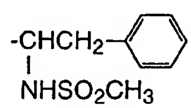
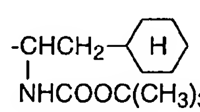
Compound No.	$-R^1\left(-D-(CH)_m-E-R^4\right)$ with R^5 on CH	$-R^2$	$-R^3$	n	A	Broken line
719	$-CHCH_2C(CH_3)_3$ / $NHCOOC_2H_5$	-H	$-NHC(=NOCOOCH_3)NH_2$	1	C	——
720	$-CHCH_2C(CH_3)_3$ / $NHSO_2CH_3$	-H	$-NHC(=NOCOOCH_3)NH_2$	1	C	——
721		-H	$-NHC(=NOH)NH_2$	1	C	Single bond
722		-H	$-NHC(=NOH)NH_2$	1	C	Single bond
723		-H	$-NHC(=NOH)NH_2$	1	C	Single bond
724		-H	$-NHC(=NOH)NH_2$	1	C	Single bond
725	$-CHCH_2C(CH_3)_3$ / $NHCOOC_2H_5$	-H	$-NHC(=NOH)NH_2$	1	C	Single bond
726	$-CHCH_2C(CH_3)_3$ / $NHSO_2CH_3$	-H	$-NHC(=NOH)NH_2$	1	C	Single bond
727		-H	$-NHC(=NOH)NH_2$	1	C	——

Table 1 (continued)

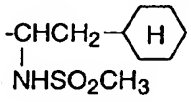
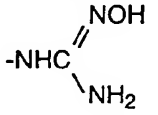
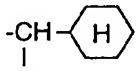
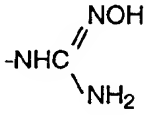
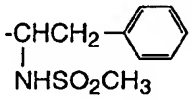
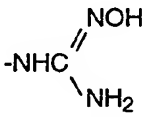
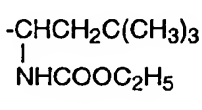
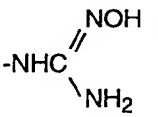
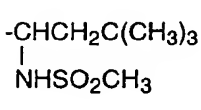
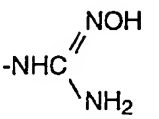
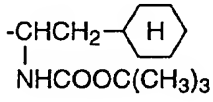
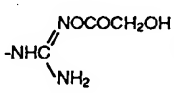
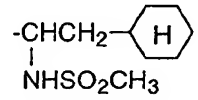
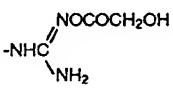
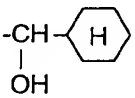
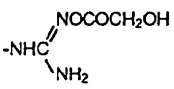
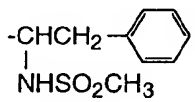
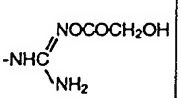
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
728		-H		1	C	——
729		-H		1	C	——
730		-H		1	C	——
731		-H		1	C	——
732		-H		1	C	——
733		-H		1	C	Single bond
734		-H		1	C	Single bond
735		-H		1	C	Single bond
736		-H		1	C	Single bond

Table 1 (continued)

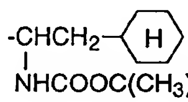
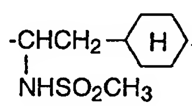
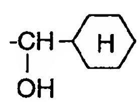
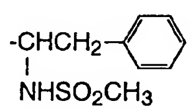
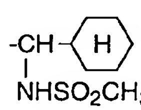
Compound No.	$-R^1\left(-D-(\underset{R^5}{CH})_m-E-R^4\right)$	$-R^2$	$-R^3$	n	A	Broken line
737	$-CHCH_2C(CH_3)_3$ $NHCOOC_2H_5$	-H	$-NHC(=NOCOCH_2OH)NH_2$	1	C	Single bond
738	$-CHCH_2C(CH_3)_3$ $NHSO_2CH_3$	-H	$-NHC(=NOCOCH_2OH)NH_2$	1	C	Single bond
739		-H	$-NHC(=NOCOCH_2OH)NH_2$	1	C	——
740		-H	$-NHC(=NOCOCH_2OH)NH_2$	1	C	——
741		-H	$-NHC(=NOCOCH_2OH)NH_2$	1	C	——
742		-H	$-NHC(=NOCOCH_2OH)NH_2$	1	C	——
743	$-CHCH_2C(CH_3)_3$ $NHCOOC_2H_5$	-H	$-NHC(=NOCOCH_2OH)NH_2$	1	C	——
744	$-CHCH_2C(CH_3)_3$ $NHSO_2CH_3$	-H	$-NHC(=NOCOCH_2OH)NH_2$	1	C	——
745		-H	$-NH_2$	1	C	Single bond

Table 1 (continued)

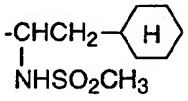
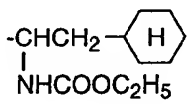
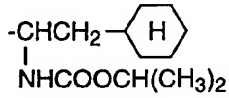
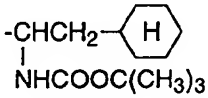
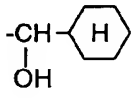
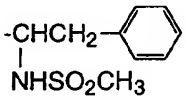
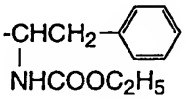
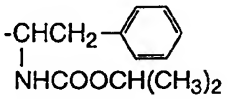
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \vert\\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
746		-H	$-NH_2$	1	C	Single bond
747		-H	$-NH_2$	1	C	Single bond
748		-H	$-NH_2$	1	C	Single bond
749		-H	$-NH_2$	1	C	Single bond
750		-H	$-NH_2$	1	C	Single bond
751		-H	$-NH_2$	1	C	Single bond
752		-H	$-NH_2$	1	C	Single bond
753		-H	$-NH_2$	1	C	Single bond

Table 1 (continued)

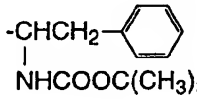
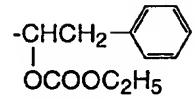
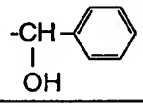
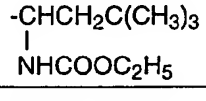
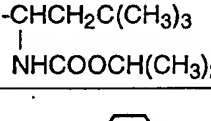
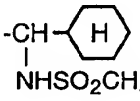
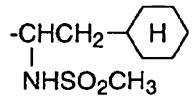
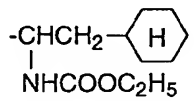
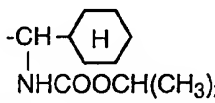
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
754		-H	$-NH_2$	1	C	Single bond
755		-H	$-NH_2$	1	C	Single bond
756		-H	$-NH_2$	1	C	Single bond
757		-H	$-NH_2$	1	C	Single bond
758		-H	$-NH_2$	1	C	Single bond
759		-H	$-NH_2$	1	C	——
760		-H	$-NH_2$	1	C	——
761		-H	$-NH_2$	1	C	——
762		-H	$-NH_2$	1	C	——

Table 1 (continued)

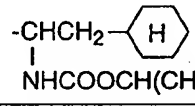
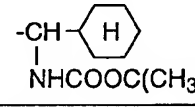
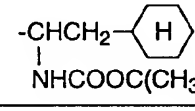
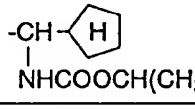
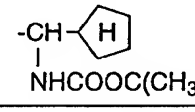
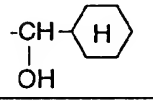
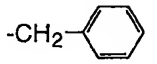
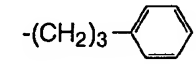
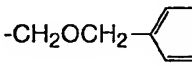
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \vert\\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
763		-H	$-NH_2$	1	C	——
764		-H	$-NH_2$	1	C	——
765		-H	$-NH_2$	1	C	——
766		-H	$-NH_2$	1	C	——
767		-H	$-NH_2$	1	C	——
768		-H	$-NH_2$	1	C	——
769		-H	$-NH_2$	1	C	——
770		-H	$-NH_2$	1	C	——
771		-H	$-NH_2$	1	C	——

Table 1 (continued)

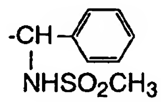
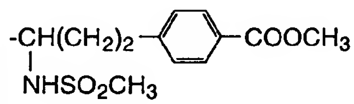
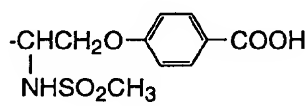
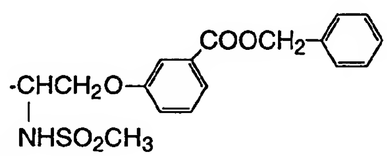
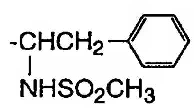
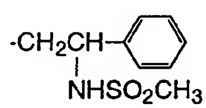
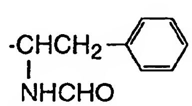
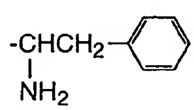
Compound No.	$-R^1\left(\begin{matrix}-D-(\underset{\displaystyle R^5}{\underset{\mid}{CH}})_m-E-R^4\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
772		-H	$-NH_2$	1	C	——
773		-H	$-NH_2$	1	C	——
774		-H	$-NH_2$	1	C	——
775		-H	$-NH_2$	1	C	——
776		-H	$-NH_2$	1	C	——
777		-H	$-NH_2$	1	C	——
778		-H	$-NH_2$	1	C	——
779		-H	$-NH_2$	1	C	——

Table 1 (continued)

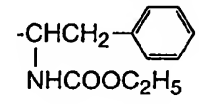
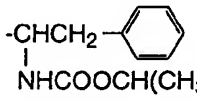
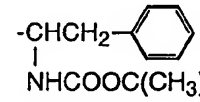
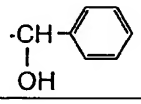
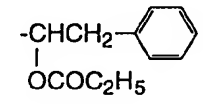
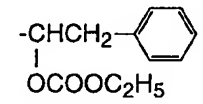
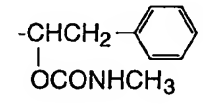
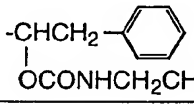
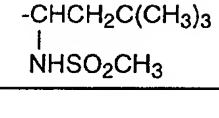
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \vert \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
780		-H	$-NH_2$	1	C	——
781		-H	$-NH_2$	1	C	——
782		-H	$-NH_2$	1	C	——
783		-H	$-NH_2$	1	C	——
784		-H	$-NH_2$	1	C	——
785		-H	$-NH_2$	1	C	——
786		-H	$-NH_2$	1	C	——
787		-H	$-NH_2$	1	C	——
788		-H	$-NH_2$	1	C	——

Table 1 (continued)

Compound No.	$-R^1\left(-D-(CH)_m-E-R^4, R^5\right)$	$-R^2$	$-R^3$	n	A	Broken line
789	$-CH(CH_2)_2SCH_3$, $NHSO_2CH_3$	-H	$-NH_2$	1	C	——
790	$-CH(CH_2)_3CH_3$, $NHSO_2CH_3$	-H	$-NH_2$	1	C	——
791	$-CH(CH_2)_4CH_3$, $NHSO_2CH_2COOH$	-H	$-NH_2$	1	C	——
792	$-CH(CH_2)_2COOH$, $NHSO_2$-C$_6$H$_5$	-H	$-NH_2$	1	C	——
793	$-CHC(SCH_3)(CH_3)_2$, $NHCOOC_2H_5$	-H	$-NH_2$	1	C	——
794	$-CHCH_2C(CH_3)_3$, $NHCOOC_2H_5$	-H	$-NH_2$	1	C	——
795	$-CHCH_2CH(C_2H_5)_2$, $NHCOOC_2H_5$	-H	$-NH_2$	1	C	——
796	$-CH(CH_2)_4CH_3$, $NHCOOC_2H_5$	-H	$-NH_2$	1	C	——
797	$-CHCH_2C(CH_3)_3$, $NHCOOCH(CH_3)_2$	-H	$-NH_2$	1	C	——
798	$-CHCH_2CH(C_2H_5)_2$, $NHCOOCH(CH_3)_2$	-H	$-NH_2$	1	C	——

Table 1 (continued)

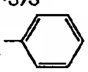
Compound No.	$-R^1\left(-D-\underset{\mid \atop R^5}{(CH)_m}-E-R^4\right)$	$-R^2$	$-R^3$	n	A	Broken line
799	$-CHCH_2C(CH_3)_3$ | $NHCOOC(CH_3)_3$	-H	$-NH_2$	1	C	——
800	$-CHCH_2CH(C_2H_5)_2$ | $NHCOOC(CH_3)_3$	-H	$-NH_2$	1	C	——
801	$-CH(CH_2)_2SCH_3$ | $NHCOOC(CH_3)_3$	-H	$-NH_2$	1	C	——
802	$-CHCH_2C(CH_3)_3$ | $NHCOOCH_2-$ 	-H	$-NH_2$	1	C	——
803	$-CHCH_2C(CH_3)_3$ | OH	-H	$-NH_2$	1	C	——
804	$-CHCH_2C(CH_3)_3$ | $OCOOC_2H_5$	-H	$-NH_2$	1	C	——
805	$-CHCH_2CH(CH_3)_2$ | $NHSO_2CH_3$	-H	$-NH_2$	1	C	——
806	$-CHCH(CH_3)_2$ | $NHSO_2CH_3$	-H	$-NH_2$	1	C	——
807	$-CHC(CH_3)_3$ | $NHSO_2CH_3$	-H	$-NH_2$	1	C	——
808	$-CHCH_2SC(CH_3)_3$ | $NHSO_2CH_3$	-H	$-NH_2$	1	C	——

Table 1 (continued)

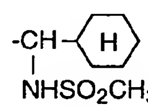
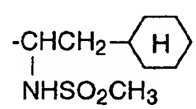
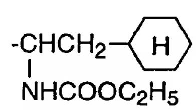
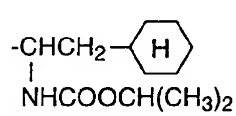
Compound No.	$-R^1\left(-D-(\underset{R^5}{\underset{\vert}{C}}H)_m-E-R^4\right)$	-R²	-R³	n	A	Broken line
809	$-\underset{NHSO_2CH_3}{\underset{\vert}{C}}HCH_2OC(CH_3)_3$	-H	$-NH_2$	1	C	——
810	$-\underset{NHSO_2CH_3}{\underset{\vert}{C}}HCH_2OC(CH_3)_2C_2H_5$	-H	$-NH_2$	1	C	——
811	$-\underset{NHSO_2CH_3}{\underset{\vert}{C}}HCH_2O(C_2H_5)_2CH_3$	-H	$-NH_2$	1	C	——
812	$-\underset{NHSO_2CH_3}{\underset{\vert}{C}}HC(CH_3)_2SCH_3$	-H	$-NH_2$	1	C	——
813	$-\underset{NHSO_2CH_3}{\underset{\vert}{C}}HC(CH_3)_2SC_2H_5$	-H	$-NH_2$	1	C	——
814		-H	$-NH_2$	2	C	Single bond
815		-H	$-NH_2$	2	C	Single bond
816		-H	$-NH_2$	2	C	Single bond
817		-H	$-NH_2$	2	C	Single bond

Table 1 (continued)

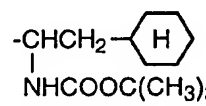
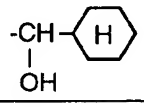
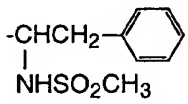
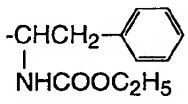
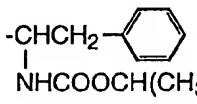
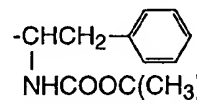
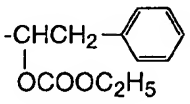
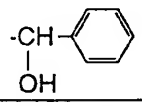
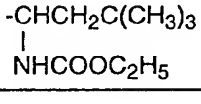
Compound No.	$-R^1\left(\begin{array}{c}-D-(CH)_m-E-R^4\\ \\ R^5\end{array}\right)$	$-R^2$	$-R^3$	n	A	Broken line
818		-H	$-NH_2$	2	C	Single bond
819		-H	$-NH_2$	2	C	Single bond
820		-H	$-NH_2$	2	C	Single bond
821		-H	$-NH_2$	2	C	Single bond
822		-H	$-NH_2$	2	C	Single bond
823		-H	$-NH_2$	2	C	Single bond
824		-H	$-NH_2$	2	C	Single bond
825		-H	$-NH_2$	2	C	Single bond
826		-H	$-NH_2$	2	C	Single bond

Table 1 (continued)

Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
827	$-CHCH_2C(CH_3)_3$ $NHCOOCH(CH_3)_2$	-H	$-NH_2$	2	C	Single bond
828	$-CH-$(H) $NHSO_2CH_3$	-H	$-NH_2$	2	C	——
829	$-CHCH_2-$(H) $NHSO_2CH_3$	-H	$-NH_2$	2	C	——
830	$-CHCH_2-$(H) $NHCOOC_2H_5$	-H	$-NH_2$	2	C	——
831	$-CHCH_2-$(H) $NHCOOCH(CH_3)_2$	-H	$-NH_2$	2	C	——
832	$-CHCH_2-$(H) $NHCOOC(CH_3)_3$	-H	$-NH_2$	2	C	——
833	$-CH-$(H) OH	-H	$-NH_2$	2	C	——
834	$-CHCH_2-$(C6H5) $NHSO_2CH_3$	-H	$-NH_2$	2	C	——
835	$-CHCH_2-$(C6H5) $NHCOOC_2H_5$	-H	$-NH_2$	2	C	——

Table 1 (continued)

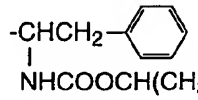
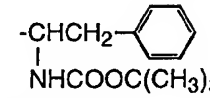
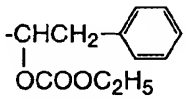
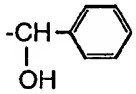
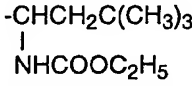
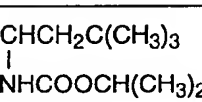
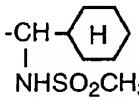
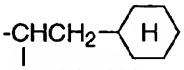
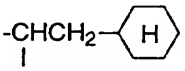
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
836		-H	$-NH_2$	2	C	——
837		-H	$-NH_2$	2	C	——
838		-H	$-NH_2$	2	C	——
839		-H	$-NH_2$	2	C	——
840		-H	$-NH_2$	2	C	——
841		-H	$-NH_2$	2	C	——
842		$-CH_3$	$-NH_2$	1	C	Single bond
843		$-CH_3$	$-NH_2$	1	C	Single bond
844		$-CH_3$	$-NH_2$	1	C	Single bond

Table 1 (continued)

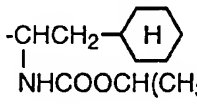
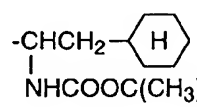
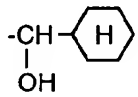
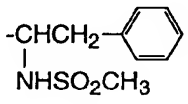
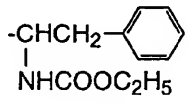
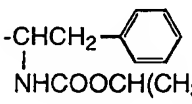
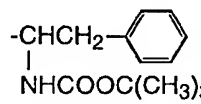
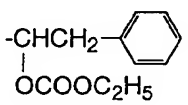
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \vert\\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
845		$-CH_3$	$-NH_2$	1	C	Single bond
846		$-CH_3$	$-NH_2$	1	C	Single bond
847		$-CH_3$	$-NH_2$	1	C	Single bond
848		$-CH_3$	$-NH_2$	1	C	Single bond
849		$-CH_3$	$-NH_2$	1	C	Single bond
850		$-CH_3$	$-NH_2$	1	C	Single bond
851		$-CH_3$	$-NH_2$	1	C	Single bond
852		$-CH_3$	$-NH_2$	1	C	Single bond

Table 1 (continued)

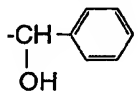
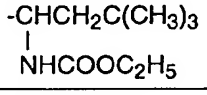
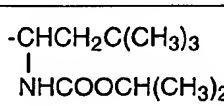
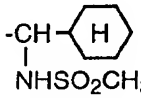
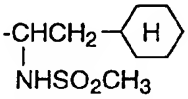
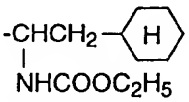
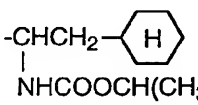
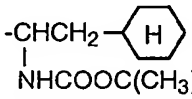
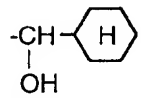
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
853		$-CH_3$	$-NH_2$	1	C	Single bond
854		$-CH_3$	$-NH_2$	1	C	Single bond
855		$-CH_3$	$-NH_2$	1	C	Single bond
856		$-CH_3$	$-NH_2$	1	C	——
857		$-CH_3$	$-NH_2$	1	C	——
858		$-CH_3$	$-NH_2$	1	C	——
859		$-CH_3$	$-NH_2$	1	C	——
860		$-CH_3$	$-NH_2$	1	C	——
861		$-CH_3$	$-NH_2$	1	C	——

Table 1 (continued)

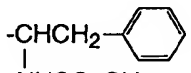
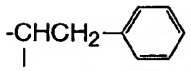
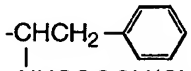
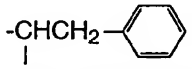
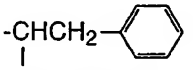
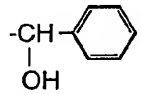
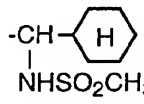
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
862		$-CH_3$	$-NH_2$	1	C	——
863		$-CH_3$	$-NH_2$	1	C	——
864		$-CH_3$	$-NH_2$	1	C	——
865		$-CH_3$	$-NH_2$	1	C	——
866		$-CH_3$	$-NH_2$	1	C	——.
867		$-CH_3$	$-NH_2$	1	C	——
868	$-CHCH_2C(CH_3)_3$ $\vert$ $NHCOOC_2H_5$	$-CH_3$	$-NH_2$	1	C	——
869	$-CHCH_2C(CH_3)_3$ $\vert$ $NHCOOCH(CH_3)_2$	$-CH_3$	$-NH_2$	1	C	——
870		$-CH_3$	$-NH_2$	2	C	Single bond

Table 1 (continued)

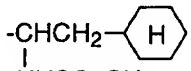
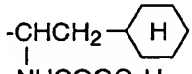
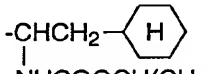
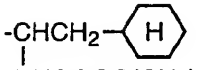
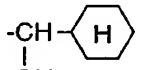
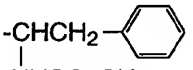
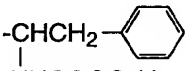
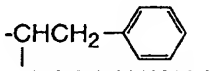
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \vert \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
871		$-CH_3$	$-NH_2$	2	C	Single bond
872		$-CH_3$	$-NH_2$	2	C	Single bond
873		$-CH_3$	$-NH_2$	2	C	Single bond
874		$-CH_3$	$-NH_2$	2	C	Single bond
875		$-CH_3$	$-NH_2$	2	C	Single bond
876		$-CH_3$	$-NH_2$	2	C	Single bond
877		$-CH_3$	$-NH_2$	2	C	Single bond
878		$-CH_3$	$-NH_2$	2	C	Single bond

Table 1 (continued)

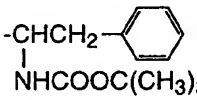
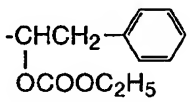
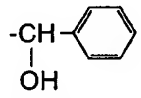
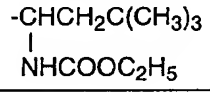
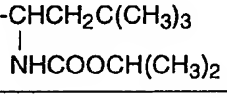
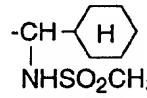
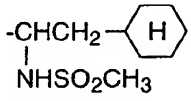
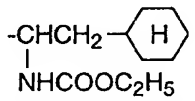
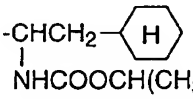
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
879		$-CH_3$	$-NH_2$	2	C	Single bond
880		$-CH_3$	$-NH_2$	2	C	Single bond
881		$-CH_3$	$-NH_2$	2	C	Single bond
882		$-CH_3$	$-NH_2$	2	C	Single bond
883		$-CH_3$	$-NH_2$	2	C	Single bond
884		$-CH_3$	$-NH_2$	2	C	——
885		$-CH_3$	$-NH_2$	2	C	——
886		$-CH_3$	$-NH_2$	2	C	——
887		$-CH_3$	$-NH_2$	2	C	——

Table 1 (continued)

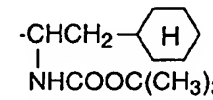
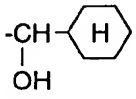
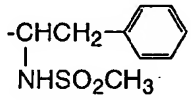
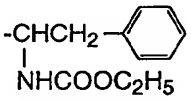
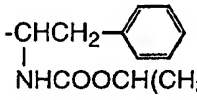
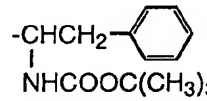
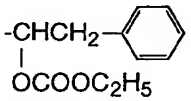
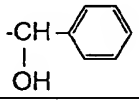
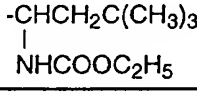
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
888		$-CH_3$	$-NH_2$	2	C	——
889		$-CH_3$	$-NH_2$	2	C	——
890		$-CH_3$	$-NH_2$	2	C	——
891		$-CH_3$	$-NH_2$	2	C	——
892		$-CH_3$	$-NH_2$	2	C	——
893		$-CH_3$	$-NH_2$	2	C	——
894		$-CH_3$	$-NH_2$	2	C	——
895		$-CH_3$	$-NH_2$	2	C	——
896		$-CH_3$	$-NH_2$	2	C	——

Table 1 (continued)

Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \vert\\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
897	$-CHCH_2C(CH_3)_3$ $\vert$ $NHCOOCH(CH_3)_2$	$-CH_3$	$-NH_2$	2	C	——
898	$-CHCH_2$–(H) $\vert$ $NHCOOC(CH_3)_3$	-H	$-NHCH_3$	1	C	Single bond
899	$-CHCH_2$–(H) $\vert$ $NHSO_2CH_3$	-H	$-NHCH_3$	1	C	Single bond
900	$-CH$–(H) $\vert$ OH	-H	$-NHCH_3$	1	C	Single bond
901	$-CHCH_2$–(C6H5) $\vert$ $NHSO_2CH_3$	-H	$-NHCH_3$	1	C	Single bond
902	$-CHCH_2C(CH_3)_3$ $\vert$ $NHCOOC_2H_5$	-H	$-NHCH_3$	1	C	Single bond
903	$-CHCH_2C(CH_3)_3$ $\vert$ $NHSO_2CH_3$	-H	$-NHCH_3$	1	C	Single bond
904	$-CHCH_2$–(H) $\vert$ $NHCOOC(CH_3)_3$	-H	$-NHCH_3$	1	C	——
905	$-CHCH_2$–(H) $\vert$ $NHSO_2CH_3$	-H	$-NHCH_3$	1	C	——

Table 1 (continued)

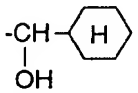
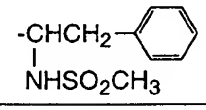
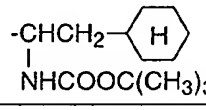
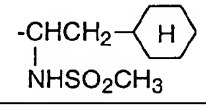
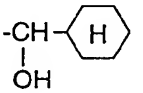
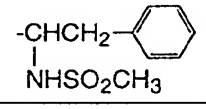
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \vert\\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
906		-H	$-NHCH_3$	1	C	——
907		-H	$-NHCH_3$	1	C	——
908	$-CHCH_2C(CH_3)_3$ $\vert$ $NHCOOC_2H_5$	-H	$-NHCH_3$	1	C	——
909	$-CHCH_2C(CH_3)_3$ $\vert$ $NHSO_2CH_3$	-H	$-NHCH_3$	1	C	——
910		-H	$-NHC_2H_5$	1	C	Single bond
911		-H	$-NHC_2H_5$	1	C	Single bond
912		-H	$-NHC_2H_5$	1	C	Single bond
913		-H	$-NHC_2H_5$	1	C	Single bond
914	$-CHCH_2C(CH_3)_3$ $\vert$ $NHCOOC_2H_5$	-H	$-NHC_2H_5$	1	C	Single bond

Table 1 (continued)

Compound No.	$-R^1\left(-D-(CH)_m-E-R^4, R^5\right)$	$-R^2$	$-R^3$	n	A	Broken line
915	$-CHCH_2C(CH_3)_3$, $NHSO_2CH_3$	-H	$-NHC_2H_5$	1	C	Single bond
916	$-CHCH_2$–H, $NHCOOC(CH_3)_3$	-H	$-NHC_2H_5$	1	C	——
917	$-CHCH_2$–H, $NHSO_2CH_3$	-H	$-NHC_2H_5$	1	C	——
918	$-CH$–H, OH	-H	$-NHC_2H_5$	1	C	——
919	$-CHCH_2$–⬡, $NHSO_2CH_3$	-H	$-NHC_2H_5$	1	C	——
920	$-CHCH_2C(CH_3)_3$, $NHCOOC_2H_5$	-H	$-NHC_2H_5$	1	C	——
921	$-CHCH_2C(CH_3)_3$, $NHSO_2CH_3$	-H	$-NHC_2H_5$	1	C	——
922	$-CHCH_2$–H, $NHCOOC(CH_3)_3$	-H	$-NHCOCH_3$	1	C	Single bond
923	$-CHCH_2$–H, $NHSO_2CH_3$	-H	$-NHCOCH_3$	1	C	Single bond

Table 1 (continued)

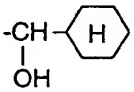
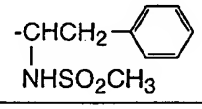
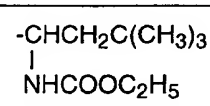
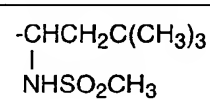
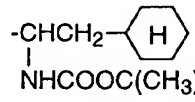
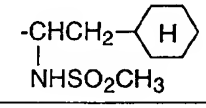
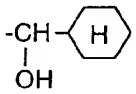
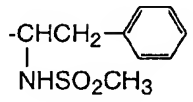
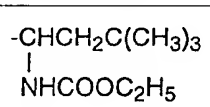
Compound No.	$-R^1\left(-D-(CH)_m-E-R^4 \atop R^5\right)$	$-R^2$	$-R^3$	n	A	Broken line
924		-H	$-NHCOCH_3$	1	C	Single bond
925		-H	$-NHCOCH_3$	1	C	Single bond
926		-H	$-NHCOCH_3$	1	C	Single bond
927		-H	$-NHCOCH_3$	1	C	Single bond
928		-H	$-NHCOCH_3$	1	C	——
929		-H	$-NHCOCH_3$	1	C	——
930		-H	$-NHCOCH_3$	1	C	——
931		-H	$-NHCOCH_3$	1	C	——
932		-H	$-NHCOCH_3$	1	C	——

Table 1 (continued)

Compound No.	$-R^1\left(-D-(CH)_m-E-R^4, R^5\right)$	$-R^2$	$-R^3$	n	A	Broken line
933	$-CHCH_2C(CH_3)_3$, $NHSO_2CH_3$	-H	$-NHCOCH_3$	1	C	——
934	$-CHCH_2$–H, $NHCOOC(CH_3)_3$	-H	$-NHCOOCH_3$	1	C	Single bond
935	$-CHCH_2$–H, $NHSO_2CH_3$	-H	$-NHCOOCH_3$	1	C	Single bond
936	$-CH$–H, OH	-H	$-NHCOOCH_3$	1	C	Single bond
937	$-CHCH_2$–C$_6$H$_5$, $NHSO_2CH_3$	-H	$-NHCOOCH_3$	1	C	Single bond
938	$-CHCH_2C(CH_3)_3$, $NHCOOC_2H_5$	-H	$-NHCOOCH_3$	1	C	Single bond
939	$-CHCH_2C(CH_3)_3$, $NHSO_2CH_3$	-H	$-NHCOOCH_3$	1	C	Single bond
940	$-CHCH_2$–H, $NHCOOC(CH_3)_3$	-H	$-NHCOOCH_3$	1	C	——
941	$-CHCH_2$–H, $NHSO_2CH_3$	-H	$-NHCOOCH_3$	1	C	——

Table 1 (continued)

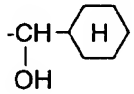
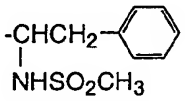
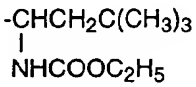
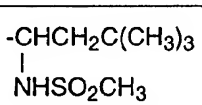
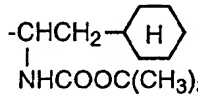
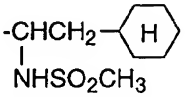
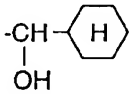
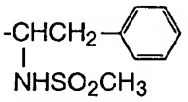
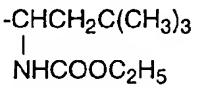
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \vert\\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
942		-H	$-NHCOOCH_3$	1	C	——
943		-H	$-NHCOOCH_3$	1	C	——
944		-H	$-NHCOOCH_3$	1	C	——
945		-H	$-NHCOOCH_3$	1	C	——
946		-H	$-NHCOOC(CH_3)_3$	1	C	Single bond
947		-H	$-NHCOOC(CH_3)_3$	1	C	Single bond
948		-H	$-NHCOOC(CH_3)_3$	1	C	Single bond
949		-H	$-NHCOOC(CH_3)_3$	1	C	Single bond
950		-H	$-NHCOOC(CH_3)_3$	1	C	Single bond

Table 1 (continued)

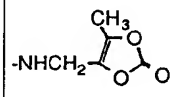
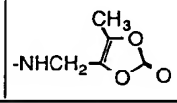
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \vert\\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
951	$-CHCH_2C(CH_3)_3$ $\vert$ $NHSO_2CH_3$	-H	$-NHCOOC(CH_3)_3$	1	C	Single bond
952	$-CHCH_2-$(H) $\vert$ $NHCOOC(CH_3)_3$	-H	$-NHCOOC(CH_3)_3$	1	C	——
953	$-CHCH_2-$(H) $\vert$ $NHSO_2CH_3$	-H	$-NHCOOC(CH_3)_3$	1	C	——
954	$-CH-$(H) $\vert$ OH	-H	$-NHCOOC(CH_3)_3$	1	C	——
955	$-CHCH_2-$(C6H5) $\vert$ $NHSO_2CH_3$	-H	$-NHCOOC(CH_3)_3$	1	C	——
956	$-CHCH_2C(CH_3)_3$ $\vert$ $NHCOOC_2H_5$	-H	$-NHCOOC(CH_3)_3$	1	C	——
957	$-CHCH_2C(CH_3)_3$ $\vert$ $NHSO_2CH_3$	-H	$-NHCOOC(CH_3)_3$	1	C	——
958	$-CHCH_2-$(H) $\vert$ $NHCOOC(CH_3)_3$	-H		1	C	Single bond
959	$-CHCH_2-$(H) $\vert$ $NHSO_2CH_3$	-H		1	C	Single bond

Table 1 (continued)

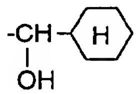
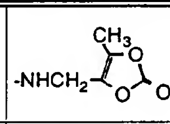
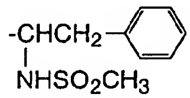
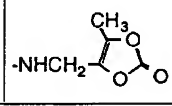
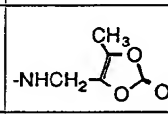
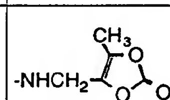
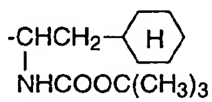
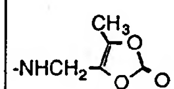
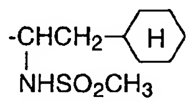
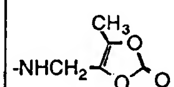
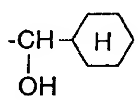
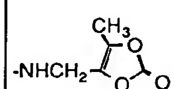
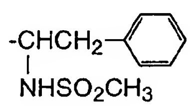
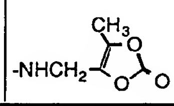
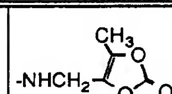
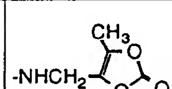
Compound No.	$-R^1\left(-D-\underset{R^5}{(CH)_m}-E-R^4\right)$	$-R^2$	$-R^3$	n	A	Broken line
960		-H		1	C	Single bond
961		-H		1	C	Single bond
962	$-CHCH_2C(CH_3)_3$ $NHCOOC_2H_5$	-H		1	C	Single bond
963	$-CHCH_2C(CH_3)_3$ $NHSO_2CH_3$	-H		1	C	Single bond
964		-H		1	C	——
965		-H		1	C	——
966		-H		1	C	——
967		-H		1	C	——
968	$-CHCH_2C(CH_3)_3$ $NHCOOC_2H_5$	-H		1	C	——
969	$-CHCH_2C(CH_3)_3$ $NHSO_2C_2H_5$	-H		1	C	——

Table 1 (continued)

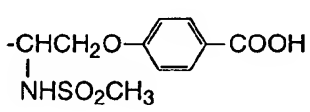
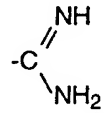
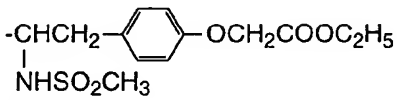
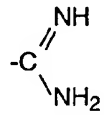
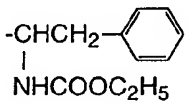
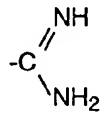
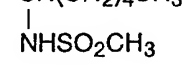
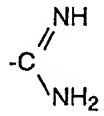
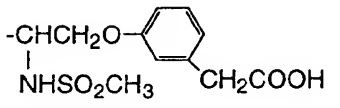
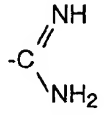
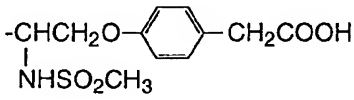
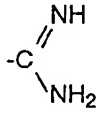
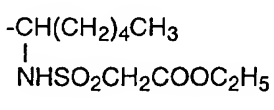
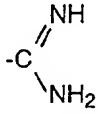
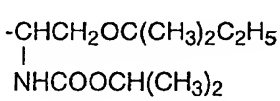
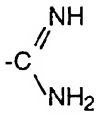
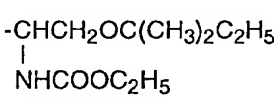
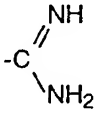
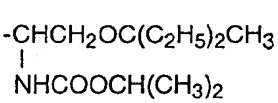
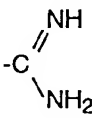
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
970		-H		1	C	Single bond
971		-H		1	C	Single bond
972		-H		1	C	Single bond
973		-H		1	C	Single bond
974		-H		1	C	Single bond
975		-H		1	C	Single bond
976		-H		1	C	Single bond
977		-H		1	C	——
978		-H		1	C	——
979		-H		1	C	——

Table 1 (continued)

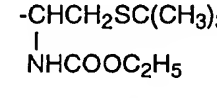
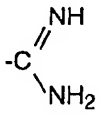
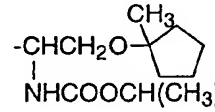
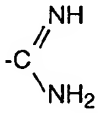
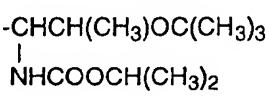
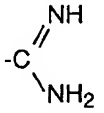
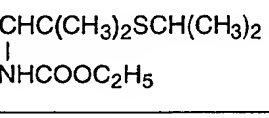
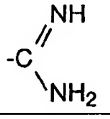
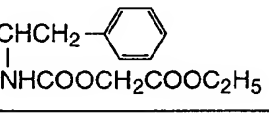
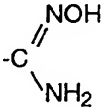
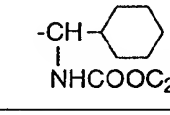
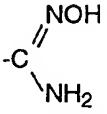
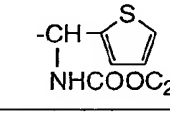
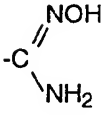
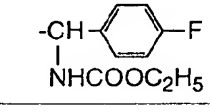
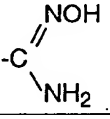
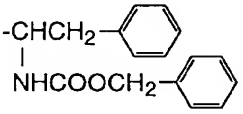
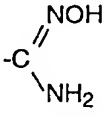
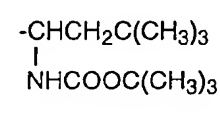
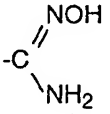
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
980		-H		1	C	——
981		-H		1	C	——
982		-H		1	C	——
983		-H		1	C	——
984		-H		1	C	Single bond
985		-H		1	C	Single bond
986		-H		1	C	Single bond
987		-H		1	C	Single bond
988		-H		1	C	Single bond
989		-H		1	C	Single bond

Table 1 (continued)

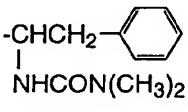
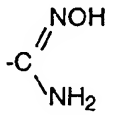
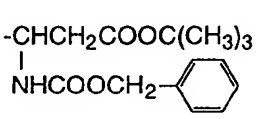
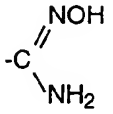
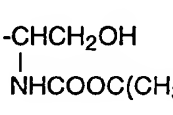
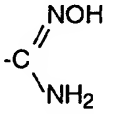
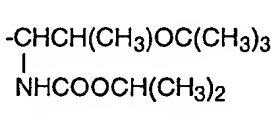
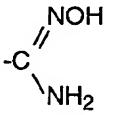
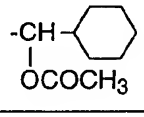
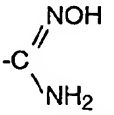
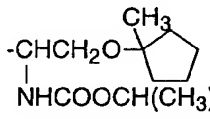
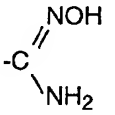
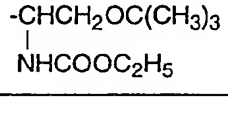
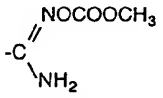
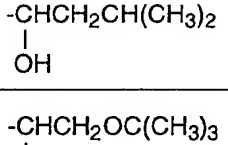
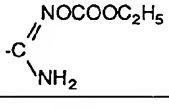
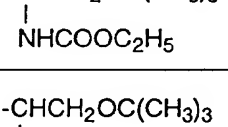
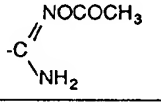
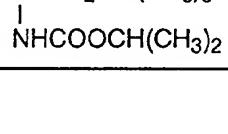
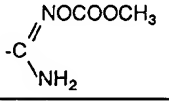
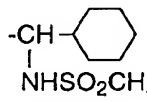
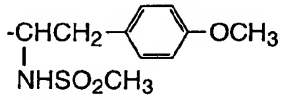
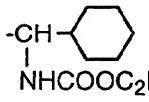
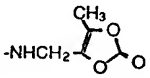
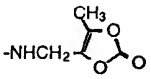
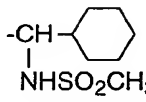
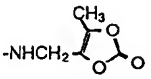
Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
990		-H		1	C	Single bond
991		-H		1	C	Single bond
992		-H		1	C	——
993		-H		1	C	——
994		-H		1	C	——
995		-H		1	C	——
996		-H		1	C	——
997		-H		1	C	——
998		-H		1	C	——
999		-H		1	C	——

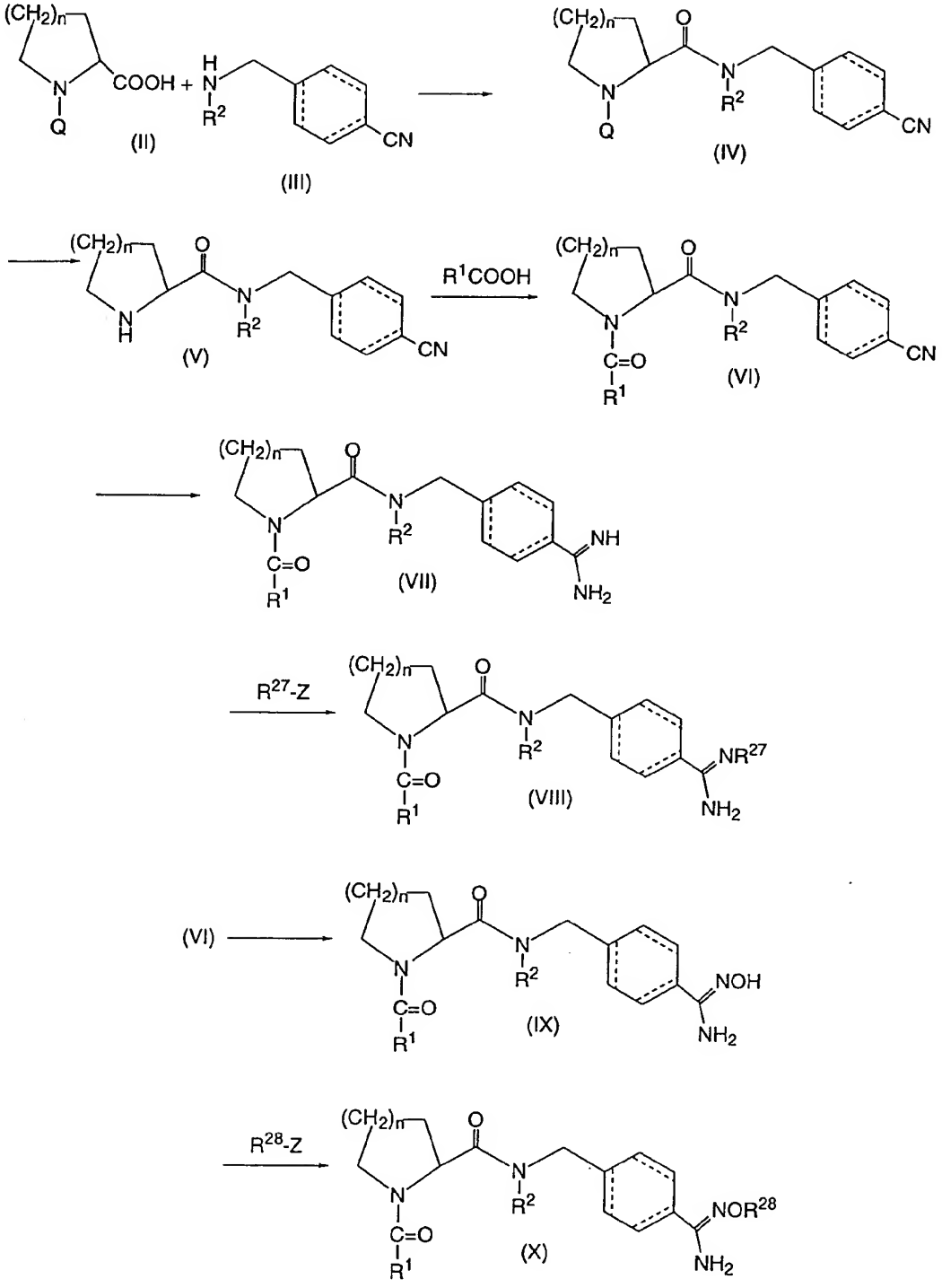
Table 1 (continued)

Compound No.	$-R^1\left(\begin{matrix}-D-(CH)_m-E-R^4\\ \\ R^5\end{matrix}\right)$	$-R^2$	$-R^3$	n	A	Broken line
1000	$-CHCH_2C(CH_3)_3$ $NHSO_2CH_3$	-H	$-C(=NCOOC_2H_5)-NH_2$	1	C	Single bond
1001		-H	$-C(=NCOOCH_3)-NH_2$	1	C	Single bond
1002		-H	$-NH_2$	1	C	——
1003	$-CHCH_2OC(CH_3)_3$ $NHCOOC_2H_5$	-H	$-NH_2$	1	C	——
1004		-H		1	C	——
1005	$-CHCH_2C(CH_3)_3$ $NHCOOCH(CH_3)_2$	-H		1	C	——
1006		-H		1	C	——

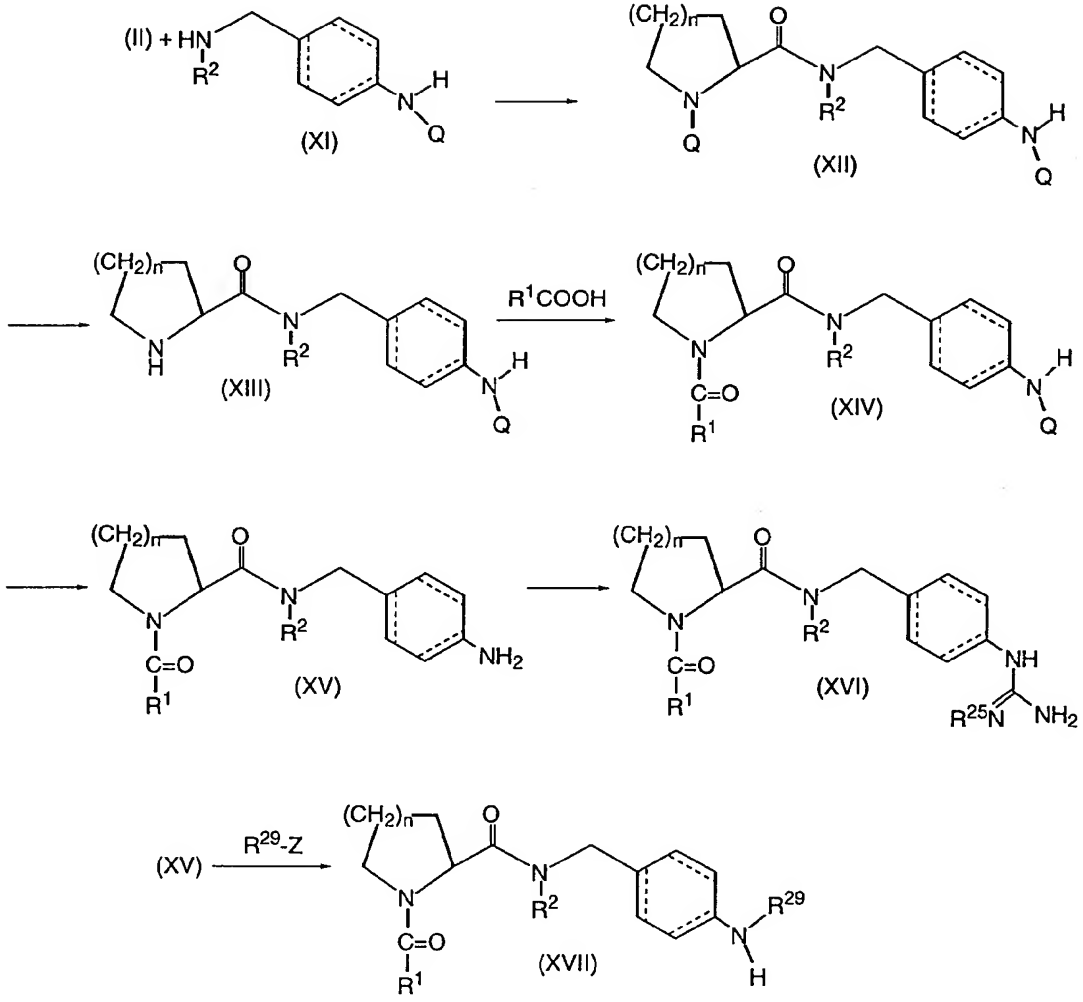
Hereinafter, the production process for the compounds of the present invention will be explained.

The compounds of the present invention can be produced through any combination of reactions suitable for the objective compounds. Typical reaction schemes will be shown below, but they should not be construed to be limiting the scope of the present invention.

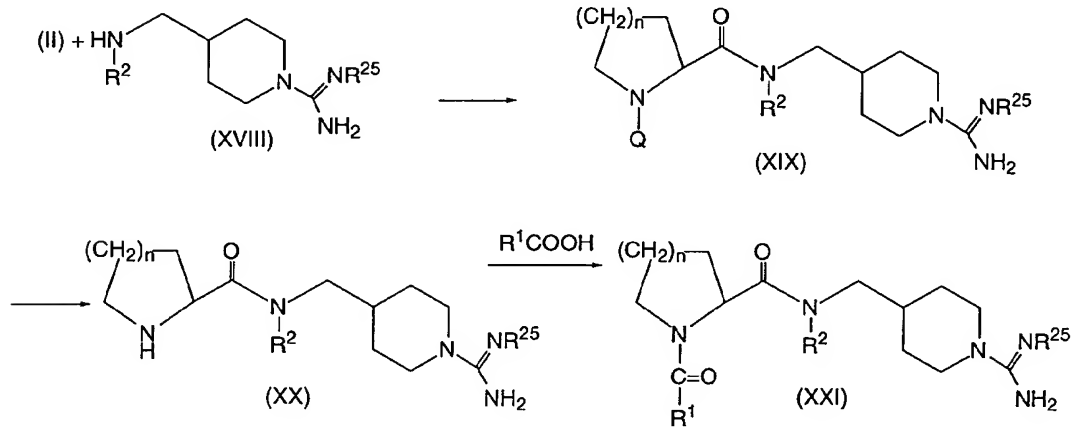
(Reaction scheme I)



(Reaction scheme II)



(Reaction scheme III)



wherein R^1, R^2, R^{25}, n and broken line are as defined above; Q is an amino-protecting group, such as benzyloxycarbonyl group, tertiary butyloxycarbonyl group, etc.; Z is a leaving group such as halogen atom, methanesulfonyloxy group, toluenesulfonyloxy group, trifluoromethylsulfonyloxy group, acetoxy (acetyloxy) group, etc.; R^{27}, R^{28} and R^{29} indicate a specific substituent contained in R^{25} and R^{26}; R^{27} is a C_1-C_6 alkyl group, a C_2-C_7 acyl group or a C_2-C_7 alkoxycarbonyl group; R^{28} is a C_1-C_6 alkyl group, a C_2-C_7 acyl group, a C_2-C_7 alkoxycarbonyl group or a C_2-C_7 hydroxyalkylcarbonyl group; R^{29} is a C_1-C_6 alkyl group, a C_2-C_7 acyl group, a C_2-C_7 alkoxycarbonyl group or 5-C_1-C_3 alkyl-1,3-dioxol-2-on-4-ylmethyl group.

In the above reaction schemes, a known method for synthesizing amide can be used for synthesizing the compounds (IV), (VI), (XII), (XIV), (XIX) and (XXI). There are vrious conventional methods, for example, a method using dehydrating agents such as dicyclohexylcarbodiimide, 1-ethyl-3-(dimethylaminopropyl)-carbodiimide, carbonyldiimidazole, etc., azido method, acid halide method, acid anhydride method, active ester method and the like.(e.q., see, "JIKKEN KAGAKU KOZA, 22, YUKI-GOSEI IV", pp. 259 - (1992), ed. "JAPAN Chemical Society", 4th. edition, published by Maruzen). The reaction is conducted under cooling or heating (or at room temperature) using an inert solvent such as tetrahydrofuran, diethyl ether, dichloromethane, etc. in a conventional manner. In the above schemes, the compounds (V), (XIII), (XV) and (XX) can be synthesized by deprotection according to a method known in the peptide chemistry (e.g. see "The Principle and Experimental Procedures of Peptide Synthesis" written by Nobuo IZUMIYA et al., published by Maruzen).

Further, the compound (VII) is synthesized by reacting imidate, which is obtained by reacting the compound (VI) with alcohol and an inorganic acid such as hydrochloric acid, with ammonia or an ammonium salt; or by reacting a thioamide compound, which is obtained by reacting the compound (VI) with hydrogen sulfide in the presence of an organic base such as triethylamine, pyridine, etc., with a lower alkylhalogen compound such as methyl iodide, etc., followed by reacting the resulting thioimidate compound with ammonia or an ammonium salt. Further, the compound (IX) is synthesized by reacting the compound (VI) with hydroxylamine or acid adduct thereof in a suitable solvent such as water, alcohol, tetrahydrofuran, etc. at room temperature or under heating.

Further, the compounds (VIII), (X) and (XVI) are synthesized by reacting the compounds (VII), (IX) and (XV) with R^{27}-Z, R^{28}-Z or R^{29}-Z in an inert solvent such as tetrahydrofuran, ether, dichloromethane, etc. in the presence of an organic or inorganic base under cooling or heating (or at room temperature), respectively.

Further, the compound (XVI) is synthesized by reacting the compound (XV) with a guanidizing reagent such as 2-alkylisothiourea derivative or acid adduct thereof in a suitable solvent such as water, alcohol, tetrahydrofuran, etc. at room temperature or under heating.

The respective compounds thus obtained can be isolated and purified by conventional chemical procedures such as extraction, crystallization, recrystallization, various chromatography and the like.

When the compounds of the present invention are used for clinical application, a proportion of a therapeutically active ingredient to a carrier component varies within a range of 1 to 90% by weight. For example, the compounds of the present invention may be orally administered in the dosage form such as granules, fine granules, powders, tablets, hard capsules, soft capsules, syrups, emulsions, suspensions, solutions and the like, or intravenously, intramuscularly or subcutaneously administered in the form of injections. Further, they may also be used in the form of suppositories. They may also be formed into powders which can be converted into solutions or the like for injection before use. There can be used pharmaceutical organic or inorganic solid or liquid carriers or diluents which are suitable for oral, intestinal or parenteral administration for preparing the drugs of the present invention. As the excipient used for preparing solid preparations, for example, there can be used lactose, sucrose, starch, talc, cellulose, dextrin, kaoline, calcium carbonate and the like. Liquid preparations for oral administration, i.e. emulsions, syrups, suspensions, solutions, etc. contain inert diluents which are normally used, e.g. water, vegetable oil, etc. This preparation can contain adjuvants such as humectants, suspension auxiliary agents, sweeteners, aromatics, colorants, preservatives, etc., in addition to inert diluents. The resulting liquid preparations may be contained in a capsule of an absorbable substance such as gelatin. As the solvent or suspending agent used for preparing preparations for parenteral administration, i.e. injections, suppositories, etc., for example, there can be used water, propylene glycol, polyethylene glycol, benzyl alcohol, ethyl oleate, lecithin and the like. As the base used for preparing suppositories, for example, there can be used cacao butter, emulsified cacao butter, laurin tallow, witepsol and the like. Preparations may be prepared by a conventional method.

The clinical dose varies depending upon age, pathology, condition of diseases and the like. For example, in the case of administering orally to an adult patient, the compounds of the present invention are normally administered with a dairy dose of about 0.01 to 1000 mg, preferably 10 to 1000 mg. The pharmaceutical composition of the present invention may be administered 1 to 3 times per day or

administered intermittently with the above dairy dose.

When using as injections, it is advantageous that the compounds of the present invention are administered continuously or intermittently to an adult patient with a single dose of 0.001 to 100 mg.

The prolineamide derivatives of the present invention or the salts thereof have a strong inhibition activity to proteases such as thrombin, trypsin and the like. The compounds of the present invention are also superior in oral absorptive action so that they are useful as oral antithrombin agents, i.e. oral anticoagulants, or oral antitrypsin agents, i.e. remedy for pancreas diseases such as pancreatitis.

The following Examples and Experimental Examples further illustrate the present invention in detail but are not to be construed to limit the scope thereof.

The conventional abbreviations used in Examples are as follows: THF:tetrahydrofuran, DMF: N,N-dimethylformamide, DMSO: dimethyl sulfoxide, CDI: carbonyldiimidazole, DPPA: diphenylphosphorylazide, Z: benzyloxycarbonyl, Boc: tertiary butyloxycarbonyl.

Further, NMR in physical properties stands for a nuclear magnetic resonance spectrum and the numeral is δ value in ppm, which is conventionally used for indicating the chemical shift. TMS (tetramethylsilane) was used as the internal standard. Further, the numeral shown in parenthesis following δ value is the number of hydrogen atoms, and the indications following the number of hydrogen atoms mean that s is singlet, d is doublet, t is triplet, q is quartet, m is multiplet, br is broad absorption peak, respectively.

IR stands for an infrared spectrum and measured as potassium bromide tablets unless otherwise stated. The numerical means the wave number in cm^{-1}. Only main absorption peak was shown. Further, mp means the non-corrected melting point in °C.

Example 1

Synthesis of 4-amidino-[(S)-N-((R)-2-methylsulfonylaminocyclohexylacetyl) prolyl]aminomethylbenzene (compound No. 105 of Table 1) hydrochloride

(a) N-4-cyanobenzylphthalimide

To a solution of potassium phthalimide (76 g, 410 mmol) in DMF (250 ml), a solution of 4-cyanobenzyl bromide (73 g, 373 mmol) in THF (250 ml) is added and stirred at 50 °C for 3 hours.

Water (500 ml) is added to the mixture and a precipitated crystal was collected. Then, the crystal is washed with water and dried to give 96 g of the titled compound (99%). mp: 189-191 °C.

(b) 4-Cyano-[(S)-prolyl]aminomethylbenzene hydrochloride

To a solution of the compound (39 g, 150 mmol) obtained in the item (a) in methanol (250 ml), hydrazine hydrate (9 ml) is added and refluxed for 6 hours. After the solvent is evaporated, an aqueous 40% sodium hydroxide solution (300 ml) is added to the residue and stirred.

The reaction mixture is extracted with toluene and the organic layer is washed once with water and saturated brine, successively, and then dried over sodium sulfate. The solvent is evaporated and the resulting crude product (15 g, 73%) is used for the next step.

To a solution of (S)-N-Boc-proline (23.7 g, 110 mmol) in THF (250 ml), CDI (17.8 g, 110 mmol) is added at 0 °C.

After the reaction solution is stirred for 2 hours, a solution of the crude product obtained in the above reaction in THF (150 ml) is added. After stirring for 6 hours, the solvent is evaporated and water (300 ml) is added to the residue. The mixture is extracted with chloroform and the organic layer is washed three times with water and once with saturated brine, successively. After drying over sodium sulfate, the solvent is evaporated and the residue is purified with silica gel chromatography (hexane-ethyl acetate).

The resulting oily product is dissolved in ethyl acetate (100 ml) and a 4N-hydrochloride in ethyl acetate (69 ml) is added and the mixture is stirred at 0 °C for 3 hours. The precipitated white solid is collected, washed with ethyl acetate and dried under reduced pressure to give 25.9 g of the titled compound (89%).

NMR (DMSO-d^6)

1.80-1.96 (m, 3H), 2.30-2.40 (m, 1H), 3.21 (br, 2H), 4.26 (br, 1H), 4.44 (d, 2H), 7.49 (d, 2H), 7.82 (d, 2H), 8.59 (br, 1H), 9.39 (t, 1H), 10.07 (br, 1H)

(c) 4-Cyano-[(S)-N-((R)-2-t-butyloxycarbonylamino-cyclohexylacetyl) prolyl]aminomethylbenzene

To a solution of the product (21 g, 79 mmol) obtained in the item (b) and (R)-N-t-butyloxycarbonyl-cyclohexylglycine (20.4 g, 79 mmol) in DMF (200 ml), a solution of triethylamine (22 ml, 159 mmol) and DPPA (22 g, 79 mmol) in DMF (50 ml) is added at 0 °C. The mixture is allowed to stand at room temperature and then stirred for 12 hours. Water (400 ml) is added to the reaction mixture which is extracted with toluene-ethyl acetate (1:2). The organic layer is washed three times with water and once with saturated brine, successively, and then dried over sodium sulfate. After the solvent is evaporated, the residue is purified with silica gel chromatography (chloroform-methanol) to give 26.7 g of the titled compound (72%).

NMR ($CDCl_3$)

1.01-1.43 (m, 15H), 1.65-2.38 (m, 9H), 3.57 (q, 1H), 3.96-4.06 (m, 2H), 4.47 (dq, 2H), 4.69 (d, 1H), 5.12 (d, 1H), 7.35 (d, 2H), 7.59 (d, 2H), 7.73 (t, 1H)

(d) 4-Cyano-[(S)-N-((R)-2-methylsulfonylamino-cyclohexylacetyl)prolyl] aminomethylbenzene

To a solution of the compound (26.7 g, 57 mmol) obtained in the item (c) in chloroform (50 ml), a 4-N hydrochloride in ethyl acetate (30 ml) is added at 0 °C. The mixture is stirred for 3 hours and then the solvent is evaporated. The resulting residue was dissolved in dichloromethane (250 ml) and triethylamine (19 ml) is added. Then, a solution of methanesulfonyl chloride (7.9 g, 68 mmol) in dichloromethane (50 ml) is added at 0 °C and the mixture is stirred for 3 hours. The organic layer is washed once with a saturated sodium bicarbonate solution, water and saturated brine, successively, and then dried over sodium sulfate. The resulting residue is purified with silica gel chromatography (hexane-ethyl acetate) to give 18.6 g of the titled compound (73%).

NMR ($CDCl_3$)

0.9-1.29 (m, 5H), 1.60-1.85 (m, 5H), 2.0-2.4 (m, 5H), 2.89 (s, 3H), 3.55 (q, 1H), 3.80-3.88 (m, 2H), 4.43 (d, 2H), 4.61 (d, 2H), 5.60 (d, 2H), 7.31 (t, 1H), 7.37 (d, 2H), 7.60 (d, 2H)

(e) 4-Amidino-[(S)-N-((R)-2-methylsulfonylamino-cyclohexylacetyl) prolyl]aminomethylbenzene chloride

To a solution of the compound (18.6 g, 42 mmol) obtained in the item (d) in chloroform (100 ml), a 37% hydrochloride in ethanol (100 ml) is added at 0 °C. The mixture is allowed to stand at 0 °C for 48 hours and then the solvent is evaporated. The resulting residue is dissolved in methanol (100 ml) and ammonium carbonate (16 g, 166 mmol) is added at 0 °C. After stirring for 6 hours, the solvent is evaporated and the resulting residue is purified with silica gel chromatography (chloroform-methanol) to give 5.2 g of the titled compound (73%).

NMR (DMSO-d^6)

9.39 (br, 4H), 8.66 (t, 1H), 7.81 (d, 2H), 7.48 (d, 2H), 7.40 (m, 1H), 4.47-4.14 (m, 3H), 3.90 (m, 1H), 3.71 (m, 1H), 3.59 (m, 1H), 2.79 (s, 3H), 2.13 (m, 1H), 1.88 (m, 3H), 1.69-1.53 (m, 5H), 1.14 (m, 6H)

IR: 3366, 2930, 2855, 1636, 1541, 1489, 1451, 1152

According to the same procedures described above, the compounds shown in the following Examples were synthesized.

Example 2

4-Amidino-[(S)-N-[(R)-2-methylsulfonylamino-4,4-dimethylpentanoyl] prolyl]aminomethylbenzene (compound No. 104 of Table 1) methanesulfonate

NMR (DMSO-d^6)

9.31 (br, 2H), 9.11 (br, 2H), 8.60 (t, 1H), 7.76 (d, 2H), 7.47 (d, 2H), 7.42 (d, 2H), 4.50-4.06 (m, 4H), 3.49 (m, 1H), 3.71 (m, 1H), 2.71 (s, 3H), 2.40 (s, 3H), 2.13 (m, 1H), 1.98 (m, 2H), 1.84 (m, 1H), 1.48 (d, 2H), 0.98 (s, 9H)

IR: 3274, 2957, 1640, 1208, 1150, 1049

Example 3

4-Amidino-[(S)-N [(R)-2-methylsulfonylamino-3-cyclohexylpropionyl] prolyl]aminomethylbenzene (compound No. 106 of Table 1) hydrochloride

NMR (DMSO-d^6)

9.41 (br, 2H), 9.20 (br, 2H), 8.68 (t, 1H), 7.78 (d, 2H), 7.47 (d, 2H), 7.41 (d, 2H), 4.49-4.23 (m, 3H), 4.13 (m, 1H), 3.69 (m, 1H), 3.48 (m, 1H), 2.72 (s, 3H), 2.12 (m, 1H), 1.97 (m, 1H), 1.83 (m, 2H), 1.64 (m, 5H), 1.40 (m, 2H), 1.19 (m, 4H), 0.94 (m, 2H)

IR: 3366, 2924, 1640, 1543, 1489, 1449, 1422

Example 4

4-Amidino-[(S)-N ((R)-N'-methylsulfonylphenylalanyl] prolyl] aminomethylbenzene (compound No. 108 of Table 1) methanesulfonate

NMR (DMSO-d^6)

9.31 (br, 2H), 9.08 (br, 2H), 8.57 (t, 1H), 7.75 (d, 2H), 7.71 (d, 1H), 7.47 (d, 2H), 7.29 (m, 5H), 4.52-4.21 (m, 3H), 3.54 (m, 2H), 3.28 (m, 2H), 3.04 (m, 1H), 2.90 (m, 2H), 2.71 (s, 3H), 2.50 (s, 3H), 1.88 (m, 2H)

IR: 3375, 1663, 1630, 1454, 1327, 1225, 1154, 1046

Example 5

4-Amidino-[(S)-N-[(R)-N'-methylsulfonylmethionyl] prolyl] aminomethylbenzene (compound No. 110 of Table 1) hydrochloride

NMR (DMSO-d^6)

9.45 (br, 2H), 9.26 (br, 2H), 8.68 (t, 1H), 7.80 (d, 2H), 7.55 (d, 2H), 7.48 (d, 2H), 4.44-4.17 (m, 4H), 3.70 (m, 1H), 3.59 (m, 1H), 2.87 (s, 3H), 2.56 (m, 3H), 2.13 (m, 1H), 2.08 (s, 3H), 1.97 - 1.63 (m, 4H)

IR: 3368, 1638, 1543, 1489, 1426, 1314, 1150

Example 6

4-Amidino-[(S)-N-((R)-N'-formylphenylalanyl) prolyl] aminomethylbenzene (compound No. 94 of Table 1) hydrochloride

NMR (DMSO-d^6)

9.56 (br, 2H), 9.36 (br, 2H), 8.97 (t, 1H), 8.70 - 8.60 (m, 1H), 7.86 (d, 1H), 7.83 (d, 2H), 7.46 (d, 2H), 7.37-7.17 (m, 5H), 4.36-4.16 (m, 4H), 3.60 - 2.70 (m, 4H), 2.40-1.20 (m, 4H)

IR: 3370, 1647, 1541, 1489, 1454, 1404, 704

Example 7

4-Amidino-[(S)-N-((R)-2-methylsulfonylamino-hexanoyl) prolyl] aminomethylbenzene (compound No. 109 of Table 1) methanesulfonate

NMR (DMSO-d^6)

9.32 (br, 2H), 9.11 (br, 2H), 8.58 (t, 1H), 7.76 (d, 2H), 7.48 (d, 2H), 7.42 (d, 1H), 4.47-4.23 (m, 2H), 4.20-3.90 (m, 3H), 3.54-3.45 (m, 1H), 3.80-3.66 (m, 1H), 2.74 (s, 3H), 2.43 (s, 3H), 2.20-0.79 (m, 13H)

IR: 3272, 1638, 1543, 1424, 1316, 1206, 1155, 1047

Example 8

4-Amidino-[(S)-N-((R)-2-methylsulfonylamino-4-(4'-methoxy-carbonylphenyl) butanoyl) prolyl]-aminomethylbenzene (compound No. 127 of Table 1) hydrochloride

NMR (DMSO-d^6)

9.35-9.23 (m, 4H), 8.59 (t, 1H), 7.90 (d, 2H), 7.77 (d, 2H), 7.61 (d, 1H), 7.47 (d, 2H), 7.40 (d, 2H), 4.44-

4.21 (m, 3H), 4.07 (m, 1H), 3.84 (s, 3H), 3.48 (m, 2H), 2.92-2.63 (m, 3H), 2.77 (s, 3H), 2.12 (m, 1H), 1.84 (m, 4H)
IR: 3370, 1638, 1541, 1489, 1437, 1287, 1150

Example 9

4-Amidino-[(S)-N-[(R)-2-methylsulfonylamino-3-(3'-carboxyphenoxy) propanoyl] prolyl]aminomethylbenzene (compound No. 130 of Table 1) hydrochloride

NMR (DMSO-d^6)
9.35 (br, 4H), 8.64 (t, 1H), 7.78 (d, 2H), 7.71 (d, 1H), 7.58-7.40 (m, 5H), 7.20 (m, 1H), 4.62 (m, 1H), 4.36 (m, 3H), 4.22 (m, 2H), 3.72 (m, 2H), 2.89 (s, 3H), 2.12 (m, 1H), 1.94 (m, 3H)
IR: 3856, 1644, 1543, 1489, 1449, 1316, 1256, 1154

Example 10

4-Amidino-[(S)-N-[(R)-2-ethylsulfonylamino-3-(2'-benzyloxycarbonylphenoxy) propanoyl] prolyl]-aminomethylbenzene (compound No. 123 of Table 1) hydrochloride

NMR (DMSO-d^6)
9.24 (br, 4H), 8.60 (t, 1H), 7.77 (d, 2H), 7.71 (m, 1H), 7.57 (m, 1H), 7.49-7.35 (m, 8H), 7.16 (d, 1H), 7.07 (t, 1H), 5.29 (s, 2H), 4.62 (t, 1H), 4.37 (m, 3H), 4.28 (m, 1H), 4.17 (t, 1H), 3.67 (m, 2H), 2.91 (s, 3H), 2.15 (m, 1H), 1.88 (m, 3H)
IR: 3366, 1642, 1491, 1451, 1314, 1248, 1082

Example 11

4-Amidino-[(S)-N-[(R)-2-ethoxycarbonylamino-3-methyl-3-methylthiobutanoyl] prolyl]aminomethylbenzene (compound No. 98 of Table 1) hydrochloride

NMR (DMSO-d^6)
8.89 (br, 2H), 8.66 (br, 2H), 7.77 (d, 2H), 7.33 (d, 2H), 6.27 (d, 1H), 4.65 (m, 1H), 4.46 (d, 1H), 4.37 (m, 2H), 3.97-3.72 (m, 4H), 2.62 (m, 1H), 2.15 (br, 3H), 2.04 (s, 3H), 1.40 (s, 3H), 1.36 (s, 3H), 1.05 (t, 3H)
IR: 3323, 2926, 1635, 1535, 1439, 1242, 1055

Example 12

4-Amidino-[(S)-N-[(R)-2-carboxymethylsulfonylaminoheptanoyl] prolyl] aminomethylbenzene (compound No. 152 of Table 1) hydrochloride

NMR (DMSO-d^6)
9.80 (br, 2H), 9.23 (br, 2H), 8.80 (t, 1H), 7.69 (d, 2H), 7.42 (d, 2H), 7.23 (d, 1H), 4.51-4.17 (m, 5H), 3.70 (m, H), 2.11 (m, 1H), 1.92 (m, 3H), 1.57-1.28 (m, 8H), 0.87 (m, 3H)
IR: 3366, 2957, 1636, 1543, 1489, 1416, 1318, 1136

Example 13

4-Amidino-[(S)-N-(4-phenylbutanoyl)prolyl] aminomethylbenzene (compound No. 3 of Table 1) hydrochloride

NMR (DMSO-d^6)
9.39 (br, 2H), 9.22 (br, 2H), 8.55 (t, 1H), 7.80 (d, 2H), 7.48 (d, 2H), 7.31-7.13 (m, 5H), 4.37-4.30 (m, 3H), 3.60-3.30 (m, 2H), 2.60 (t, 2H), 2.34-1.75 (m, 8H)
IR: 3264, 1618, 1541, 1491, 1451, 702

Example 14

4-Amidino-[(S)-N-(2-benzyloxyacetyl)prolyl] aminomethylbenzene (compound No. 55 of Table 1) hydrochloride

NMR (DMSO-d^6)

9.41 (br, 2H), 9.23 (br, 2H), 8.66 (t, 1H), 7.80 (d, 2H), 7.49 (d, 2H), 7.42-7.27 (m, 5H), 4.61-4.08 (m, 7H), 3.56-3.40 (m, 2H), 2.20-1.78 (m, 4H)

IR: 3262, 1645, 1539, 1489, 1454, 740

Example 15

Trans-4-amidino-[(S)-N-[(R)-2-ethoxycarbonylamino-4,4-dimethylpentanoyl]prolyl] aminomethylcyclohexane (compound No. 263 of Table 1) hydrochloride

(a) Trans-4-N-benzyloxycarbonylaminomethyl-cyclohexylnitrile

To a solution of trans-4-aminomethylcyclohexanecarboxylic acid (25 g, 159 mmol) and sodium carbonate (20 g, 191 mmol) in water (300 ml), benzyloxycarbonyl chloride (27 ml, 190 mmol) is added at 0 °C. After stirring for 6 hours, 1N-hydrochloric acid is added until the pH of the reaction mixture indicates 2, and the precipitated white solid is collected, washed with water and dried. The resulting white solid is dissolved in THF (300 ml) and CDI (21 g, 130 mmol) is added at 0 °C. After stirring for 3 hours, the reaction mixture is added dropwise to a mixed solution of 33% ammonia in water (50 ml) and THF (150 ml) at 0 °C. After stirring for 5 hours, the solvent is evaporated and water (500 ml) is added, and the precipitated white solid is collected, washed with water and dried.

To a solution of the resulting compound in 1,2-dichloroethane (500 ml), thionyl chloride (19 ml, 260 mmol) is added and heated to an inner temperature of 70 °C. After stirring for 5 hours, the reaction mixture is poured into ice water and neutralized with an aqueous 1N-sodium hydroxide solution. After extracting with chloroform, the organic layer is washed twice with water and once with saturated brine, successively, and then dried over sodium sulfate. The solvent is evaporated and the resulting crude product is recrystallized (hexane-ethyl acetate) to give 22.8 g of the titled compound (53%). mp: 90-92 °C

(b) Trans-4-(S)-prolylaminomethyl-cyclohexylnitrile

The compound obtained in the item (a) is dissolved in ethanol (250 ml) and the catalytic hydrogenation is conducted at room temperature and atomospheric pressure in the presence of palladium black (1 g). After the completion of the reaction, the catalyst is filtered off and the solvent is evaporated.

To a solution of (S)-N-benzyloxycarbonylproline (20.7 g, 83 mmol) in THF (150 ml), CDI (13.5 g, 83 mmol) is added at 0 °C. After stirring for 3 hours, a solution of the compound obtained in the above reaction in THF (200 ml) is added at 0 °C. After stirring for 12 hours, the solvent is evaporated, and chloroform (400 ml) is added to the resulting residue. The organic layer is washed three times with water and once with saturated brine, successively, and then dried over sodium sulfate. The solvent is evaporated and the resulting residue is purified with silica gel chromatography (chloroform-methanol).

The resulting compound is dissolved in ethanol (250 ml) and the catalytic hydrogenation is conducted at room temperature and atomospheric pressure in the presence of palladium black (1 g). After the completion of the reaction, the catalyst is filtered off and the solvent is evaporated to give 18.8 g of the titled compound (95%).

NMR (DMSO-d^6)

0.88-1.06 (m, 2H), 1.38-1.52 (m, 3H), 1.68-2.03 (m, 7H), 2.20-2.40 (m, 1H), 2.52-2.67 (m, 1H), 2.80-3.20 (m, 4H), 4.03-4.10 (m, 1H), 7.53 (br, 1H), 8.65-8.70 (m, 1H)

(c) Trans-4-amidino-[(S)-N-[(R)-2-ethoxycarbonylamino-4,4-dimethylpentanoyl] prolyl]-aminomethylcyclohexane hydrochloride

According to the same manner as that described in the items (c) to (e) of Example 1, the titled compound can be synthesized from the compound obtained in the item (b) and (R)-2-t-butyloxycarbonylamino-4,4-dimethylpentanoic acid.

NMR (DMSO-d^6)

8.95 (br, 2H), 8.69 (br, 2H), 7.60 (br, 1H), 6.32 (br, 1H), 4.56 (m, 1H), 4.39 (m, 1H), 4.18 (q, 2H), 4.10 (m, 1H), 3.52 (m, 1H), 3.19 (m, 1H), 2.89 (m, 1H), 2.69 (m, 1H), 2.14-1.59 (m, 12H), 1.26 (t, 3H), 0.98 (s, 9H), 0.98-0.89 (m, 2H)

IR: 3314, 2954, 1686, 1639, 1543, 1449, 1250, 1059

According to the same procedures, the compounds shown in the following Examples were synthesized.

Example 16

Trans-4-amidino-[(S)-N-[(R)-2-ethoxycarbonylamino-3-cyclohexylpropanoyl] prolyl]aminoethylcyclohexane (compound No. 227 of Table 1) hydrochloride

NMR (DMSO-d^6)

8.93 (br, 2H), 8.81 (br, 2H), 7.53 (br, 1H), 7.38 (t, 1H), 4.50-4.15 (m, 1H), 4.10-3.90 (m, 2H), 3.73-3.17 (m, 2H), 3.05-2.80 (m, 3H), 2.39 (br, 1H), 2.00-0.68 (m, 29H)

IR: 3297, 2926, 2853, 1684, 1543, 1449, 1262, 1053

Example 17

Trans-4-amidino-[(S)-N-[(R)-2-isopropoxycarbonylamino-4,4-dimethylpentanoyl] prolyl]-aminomethylcyclohexane (compound No. 265 of Table 1) hydrochloride

NMR (DMSO-d^6)

8.91 (br, 2H), 8.78 (br, 2H), 7.55 (br, 1H), 7.28 (t, 1H), 4.78-4.70 (m, 1H), 4.30-3.92 (m, 1H), 3.80-3.20 (m, 3H), 3.0-2.75 (m, 2H), 2.50-1.37 (m, 14H), 1.18-1.00 (m, 6H), 1.0-0.81 (m, 1H)

IR: 3285, 2953, 2870, 1684, 1541, 1449, 1250, 1111

Example 18

Trans-4-amidino-[(S)-N-((R)-N'-methylsulfonylphenylalanyl) prolyl] aminomethylcyclohexane (compound No. 250 of Table 1) hydrochloride

NMR (DMSO-d^6)

8.88 (br, 2H), 8.75 (br, 2H), 7.85 (t, 1H), 7.65 (d, 1H), 4.27 (m, 1H), 4.16 (m, 1H), 3.51-3.41 (m, 4H), 2.99-2.70 (m, 4H), 2.78 (s, 3H), 2.38 (t, 1H), 1.90-1.40 (m, 9H), 1.08-0.87 (m, 2H)

IR: 3375, 2930, 1637, 1452, 1309, 1149, 1097, 983

Example 19

Trans-4-amidino-[(S)-N-((R)-N'-methylsulfonylleucyl) prolyl] aminomethylcyclohexane (compound No. 269 of Table 1) hydrochloride

NMR (DMSO-d^6)

8.89 (br, 2H), 8.85 (br, 2H), 6.56 (d, 1H), 4.53 (m, 1H), 4.17 (m, 1H), 3.86 (m, 1H), 3.47 (m, 1H), 3.07 (m, 2H), 2.97 (s, 3H), 2.13-1.80 (m, 10H), 1.63-1.54 (m, 4H), 1.33 (m, 1H), 0.98-0.87 (m, 2H), 0.97 (d, 6H)

IR: 3261, 2932, 1639, 1450, 1313, 1143, 1087, 985

Example 20

Trans-4-amidino-[(S)-N-((R)-2-methylsulfonylamino-3-cyclohexyl-propanoyl) prolyl]aminomethylcyclohexane (compound No. 230 of Table 1) hydrochloride

NMR (DMSO-d^6)

8.95 (br, 2H), 8.53 (br, 2H), 7.27 (m, 1H), 6.51 (d, 1H), 4.51 (m, 1H), 4.19 (m, 1H), 3.83 (m, 1H), 3.66 (m, 1H), 3.41 (m, 2H), 3.04 (m, 2H), 3.04 (m, 2H), 2.95 (s, 3H), 2.46 (t, 1H), 2.12-0.92 (m, 24H)

IR: 3265, 2926, 1639, 1545, 1448, 1315, 1143, 985

Example 21

Trans-4-amidino-[(S)-N-((R)-2-isopropoxycarbonylamino-2-cyclohexylacetyl) prolyl]aminomethylcyclohexane (compound No. 228 of Table 1) hydrochloride

NMR (DMSO-d^6)

8.91 (br, 2H), 8.69 (br, 2H), 7.36 (br, 1H), 5.99 (d, 1H), 4.84-4.79 (m, 1H), 4.58 (br, 2H), 4.53-4.50 (m, 2H), 4.10-3.90 (m, 2H), 3.60-3.40 (m, 1H), 2.50-0.97 (m, 30H)

IR: 3297, 2980, 2930, 2855, 1684, 1539, 1451, 1258

Example 22

Trans-4-amidino-[(S)-N-((R)-2-ethoxycarbonylamino-4-ethyl-hexanoyl) prolyl]aminomethylcyclohexane (compound No. 264 of Table 1) hydrochloride

NMR (DMSO-d^6)

8.91 (br, 2H), 8.70 (br, 2H), 7.54 (m, 1H), 6.34 (m, 1H), 4.56 (m, 1H), 4.38 (m, 1H), 4.11 (m, 3H), 3.48 (m, 1H), 3.21 (m, 1H), 2.88 (m, 1H), 2.68 (m, 1H), 2.30-1.19 (m, 18H), 1.26 (t, 3H), 0.96 (m, 2H), 0.86 (t, 6H)

IR: 3279, 2962, 1685, 1639, 1541, 1448, 1257, 1059, 752

Example 23

Trans-4-amidino-[(S)-N-[(R)-2-t-butoxycarbonylamino-4,4-dimethylpentanoyl] prolyl]aminomethylcyclohexane (compound No. 266 of Table 1) glycolate

NMR (DMSO-d^6)

9.54 (br, 2H), 8.72 (br, 2H), 7.54 (br, 1H), 7.01 (t, 1H), 4.60-4.00 (m, 4H), 3.40 (m, 2H), 3.10-2.75 (m, 3H), 2.35 (br, 1H), 2.00-1.20 (m, 24H), 0.91 (s, 9H)

IR: 3316, 2953, 1686, 1543, 1449, 1368, 1167

Example 24

4-[(S)-N-[(R)-2-t-butyloxycarbonylamino-cyclohexylacetyl] prolyl] aminomethyl-benzamidoxime (compound No. 396 of Table 1)

To a solution of the compound (0.94 g, 2 mmol) obtained in the item (c) of Example 1 in ethanol (15 ml), a solution of sodium carbonate (0.17 g, 1.6 mmol) in water (3 ml) and hydroxyamine hydrochloride (0.22 g, 3.2 mmol) are added. After the reaction mixture is heated at reflux for 8 hours, the solvent is evaporated and the resulting residue is purified with silica gel column chromatography (chloroform-methanol) to give 0.84 g of the titled compound (84%).

NMR ($CDCl_3$)

1.0-1.49 (m, 14H), 1.5-2.4 (m, 10H), 3.56 (br, 1H), 3.97 (br, 1H), 4.09 (t, 1H), 4.41 (dq, 2H), 4.67 (d, 1H), 4.94 (br, 2H), 5.41 (d, 1H), 7.20 (d, 2H), 7.23-7.27 (m, 1H), 7.50 (d, 2H), 7.75 (br, 1H)

IR: 3345, 2978, 2930, 2855, 1640, 1528, 1449, 1167

According to the same procedures, the compounds shown in the following Examples were synthesized.

Example 25

4-[(S)-N-phenylacetylprolyl] aminomethyl-benzamidoxime (compound No. 374 of Table 1)

NMR ($CDCl_3$)

8.11 (t, 1H), 7.37 (d, 2H), 7.28-7.23 (m, 5H), 7.08 (d, 2H), 4.88 (s, 2H), 4.68 (d, 1H), 4.51 (m, 1H), 4.21 (m, 1H), 3.71 (s, 2H), 3.63-3.51 (m, 2H), 2.40-2.01 (m, 4H)

IR: 3315, 2968, 1637, 1543, 1244, 1155, 927, 709

Example 26

4-[(S)-N-[(R)-N'-ethoxycarbonylphenylalanyl] prolyl]aminomethylbenzamidoxime (compound No. 387 of Table 1)

NMR ($CDCl_3$)
7.54 (d, 2H), 7.27-7.19 (m, 7H), 6.31 (d, 1H), 5.05 (br, 2H), 4.65-4.42 (m, 3H), 4.24-4.10 (m, 1H), 3.80-3.40 (m, 3H), 3.10-2.95 (m, 2H), 2.60-2.50 (m, 1H), 2.14 (br, 1H), 1.95-1.50 (m, 3H), 0.99 (t, 3H)
IR: 3339, 1641, 1539, 1451, 1260, 752, 702

Example 27

4-[(S)-N-[(R)-2-t-butyloxycarbonylamino-3-cyclohexylpropanoyl] prolyl]aminomethyl-benzamidoxime (compound No. 397 of Table 1)

NMR ($CDCl_3$)
7.75 (br, 1H), 7.50 (d, 2H), 7.21 (d, 2H), 5.40 (d, 1H), 4.94 (br, 2H), 4.64 (br, 1H), 4.40-4.25 (m, 3H), 3.95 (br, 1H), 3.50-3.40 (m, 1H), 2.0-0.80 (m, 26H)
IR: 3337, 2978, 2924, 2851, 1642, 1536, 1449, 1167

Example 28

4-[(S)-N-[(R)-2-ethoxycarbonylamino-3-methyl-3-methylthiobutanoyl] prolyl]aminomethyl-benzamidoxime (compound No. 419 of Table 1)

NMR ($CDCl_3$)
7.66 (t, 1H), 7.53 (d, 2H), 7.23 (d, 2H), 5.64 (d, 1H), 4.91 (s, 2H), 4.68 (d, 1H), 4.58-4.30 (m, 3H), 3.90 (m, 1H), 3.87-3.76 (m, 2H), 3.62 (m, 1H), 2.37 (m, 1H), 2.09-2.00 (m, 3H), 2.06 (s, 3H), 1.41 (s, 3H), 1.39 (s, 3H), 1.09 (t, 3H)
IR: 3339, 2978, 1641, 1535, 1439, 1249, 1057, 929, 754

Example 29

4-[(S)-N-[(R)-phenylalanyl] prolyl]aminomethyl-benzamidoxime (compound No. 390 of Table 1) dihydrochloride

NMR (DMSO-d^6)
11.24 (br, 1H), 9.02 (br, 2H), 8.91 (t, 1H), 8.80 (br, 3H), 7.66 (d, 2H), 7.44 (d, 2H), 7.35-7.22 (m, 5H), 4.30-4.16 (m, 4H), 3.57-2.95 (m, 3H), 2.45-2.30 (m, 1H), 1.90-1.20 (m, 4H)
IR: 3059, 1649, 1539, 1491, 1454

Example 30

Trans-4-[(S)-N-((R)-2-isopropoxycarbonylamino-2-cyclohexylacetyl) prolyl]-aminomethylcyclohexanecarboxamidoxime (compound No. 430 of Table 1)

NMR ($CDCl_3$)
7.14 (br, 1H), 5.70 (d, 1H), 4.85-4.80 (m, 1H), 4.70-4.50 (m, 3H), 4.17-4.08 (m, 2H), 3.96 (br, 1H), 3.54 (q, 1H), 3.05 (t, 2H), 2.40-2.20 (m, 1H), 2.09-0.88 (m, 30H)
IR: 3342, 2978, 2928, 2855, 1653, 1449, 1256, 1111

Example 31

Trans-4-[(S)-N-((R)-2-t-butoxycarbonylamino-3-cyclohexylpropanoyl) prolyl]-aminomethylcyclohexanecarboxamidoxime (compound No. 435 of Table 1)

NMR ($CDCl_3$)
7.14 (br, 1H), 5.40 (d, 1H), 4.60-4.33 (m, 5H), 3.88 (br, 1H), 3.43 (q, 1H), 3.20-3.11 (m, 1H), 3.0-2.96 (m,

1H), 2.40-2.30 (m, 1H), 2.0-0.84 (m, 35H)
IR: 3356, 2926, 2853, 1649, 1537, 1448, 1167

Example 32

Trans-4-[(S)-N-((R)-2-t-butoxycarbonylamino-2-cyclohexylacetyl) prolyl]-aminomethylcyclohexanecarboxamidoxime (compound No. 433 of Table 1)

NMR ($CDCl_3$)
7.15 (br, 1H), 5.28 (d, 1H), 4.58 (br, 4H), 4.09 (t, 1H), 3.92 (br, 1H), 3.53 (q, 1H), 3.20-2.90 (m, 2H), 2.40 (br, 1H), 2.10-0.91 (m, 33H)
IR: 3347, 2930, 2855, 1649, 1541, 1451, 1169

Example 33

Trans-4-[(S)-N-[(R)-2-t-ethoxycarbonylamino-4,4-dimethylpentanoyl] prolyl]-aminomethylcyclohexanecarboxamidoxime (compound No. 461 of Table 1)

NMR ($CDCl_3$)
7.06 (t, 1H), 5.56 (d, 1H), 4.57-4.39 (m, 4H), 4.11 (q, 2H), 3.98 (m, 1H), 3.47 (m, 1H), 3.05 (m, 2H), 2.39 (m, 1H), 2.04-1.78 (m, 10H), 1.57 (d, 2H), 1.56-1.12 (m, 2H), 1.24 (t, 3H), 0.99 (s, 9H), 0.99-0.89 (m, 2H)
IR: 3356, 2934, 1649, 1541, 1446, 1249, 1059, 927

Example 34

Trans-4-[(S)-N-[(R)-2-methoxycarbonylamino-4,4-dimethylpentanoyl] prolyl]-aminomethylcyclohexanecarboxamidoxime (compound No. 458 of Table 1)

NMR ($CDCl_3$)
7.04 (t, 1H), 5.53 (d, 1H), 4.68 (s, 2H), 4.56 (d, 1H), 4.43 (m, 1H), 3.98 (m, 1H), 3.66 (s, 3H), 3.47 (m, 1H), 3.07 (m, 2H), 2.39 (m, 1H), 2.19-1.77 (m, 8H), 1.57 (d, 2H), 1.55-1.25 (m, 4H), 0.99 (s, 9H), 0.93 (m, 2H)
IR: 3344, 2949, 1712, 1649, 1548, 1448, 1249, 1059

Example 35

Trans-4-[(S)-N-[(R)-2-t-butoxycarbonylamino-4,4-dimethylpentanoyl] prolyl]-aminomethylcyclohexanecarboxamidoxime (compound No. 467 of Table 1)

NMR ($CDCl_3$)
7.12 (t, 1H), 5.14 (d, 1H), 4.58 (d, 1H), 4.53 (s, 2H), 4.37 (m, 1H), 3.92 (m, 1H), 3.45 (m, 1H), 3.19 (m, 1H), 2.95 (m, 1H), 2.42 (m, 1H), 2.06-1.79 (m, 8H), 1.53 (d, 2H), 1.52-1.34 (m, 4H), 1.43 (s, 9H), 0.99 (s, 9H), 1.00-0.89 (m, 2H)
IR: 3358, 2930, 1649, 1535, 1448, 1367, 1249, 1168

Example 36

Trans-4-[(S)-N-[(R)-2-benzyloxycarbonylamino-4,4-dimethypentanoyl] prolyl]-aminomethylcyclohexanecarboxamidoxime (compound No. 469 of Table 1)

NMR ($CDCl_3$)
7.36-7.27 (m, 5H), 7.04 (t, 1H), 5.63 (d, 1H), 5.16-5.00 (m, 2H), 4.58-4.46 (m, 4H), 3.97 (m, 1H), 3.47 (m, 1H), 3.06-2.92 (m, 2H), 2.43-2.38 (m, 1H), 2.01-1.72 (m, 8H), 1.58 (d, 2H), 1.50-1.23 (m, 4H), 0.98 (s, 9H), 0.98-0.88 (m, 2H)
IR: 3356, 2928, 1649, 1541, 1448, 1249, 1053 929

Example 37

Trans-4-[(S)-N-[(R)-2-isopropoxycarbonylamino-4,4-dimethylpentanoyl] prolyl] aminomethylcyclohexanecarboxamidoxime (compound No. 464 of Table 1)

NMR ($CDCl_3$)
7.11 (t, 1H), 5.49 (d, 1H), 4.83 (m, 1H), 4.56 (m, 3H), 4.42 (dd, 1H), 3.98 (m, 1H), 3.47 (dd, 1H), 3.04 (m, 2H), 2.40 (m, 1H), 2.01 (m, 2H), 1.92 (m, 3H), 1.80 (m, 3H), 1.57 (d, 2H), 1.39 (m, 4H), 1.21 (m, 6H), 0.99 (s, 9H), 0.94 (m, 2H)
IR: 3343, 1649, 1541, 1449, 1275

Example 38

Trans-4-[(S)-N-[(R)-2-isopropoxycarbonylamino-2-cyclopentylacetyl] prolyl]-aminomethylcyclohexanecarboxamidoxime (compound No. 464 of Table 1)

NMR ($CDCl_3$)
7.14 (t, 1H), 5.42 (d, 1H), 4.83 (m, 1H), 4.60 (d, 1H), 4.52 (s, 2H), 4.13 (m, 1H), 3.98 (m, 1H), 3.56 (m, 1H), 3.04 (m, 2H), 2.35 (m, 1H), 2.24 (m, 1H), 2.10-1.30 (m, 20H), 1.23 (dd, 6H), 1.01-0.93 (m, 2H)
IR: 3344, 2934, 1649, 1541, 1448, 1275, 1111, 754

Example 39

Trans-4-[(S)-N-((R)-2-t-butoxycarbonylamino-2-cyclopentylacetyl) prolyl]-aminomethylcyclohexanecarboxamidoxime (compound No. 432 of Table 1)

NMR ($CDCl_3$)
7.16 (t, 1H), 5.16 (d, 1H), 4.60 (d, 1H), 4.51 (s, 2H), 4.14 (t, 1H), 3.94 (m, 1H), 3.52 (m, 1H), 3.01 (m, 2H), 2.38 (m, 1H), 2.23-1.39 (m, 21H), 1.43 (s, 9H), 1.17-0.90 (m, 2H)
IR: 3350, 2932, 1649, 1541, 1448, 1367, 1251, 1167, 929

Example 40

Trans-4-[(S)-N-((R)-2-ethoxycarbonylamino-3-cyclohexylpropanoyl) prolyl]-aminomethylcyclohexanecarboxamidoxime (compound No. 428 of Table 1)

NMR ($CDCl_3$)
7.08 (br, 1H), 5.53 (d, 1H), 4.80-4.40 (m, 4H), 4.10-3.85 (m, 4H), 3.44 (q, 1H), 3.06 (t, 3H), 2.15-0.90 (m, 29H)
IR: 3343, 2926, 2853, 1649, 1541, 1449, 1260, 1053

Example 41

Trans-4-[(S)-N-((R)-2-isopropoxycarbonylamino-3-cyclohexylpropanoyl) prolyl] aminomethylcyclohexanecarboxamidoxime (compound No. 431 of Table 1)

NMR ($CDCl_3$)
7.12 (br, 1H), 5.51 (d, 1H), 4.85-4.70 (m, 1H), 4.60-4.30 (m, 4H), 4.0-3.85 (m, 1H), 3.44 (q, 1H), 3.10-2.95 (m, 3H), 2.45-2.35 (m, 1H), 2.05-0.80 (m, 32H)
IR: 3347, 2978, 2926, 2853, 1649, 1539, 1449, 1261, 1111

Example 42

Trans-4-[(S)-N-((R)-2-isopropoxycarbonylamino-4-ethyl-hexanoyl) prolyl]-aminomethylcyclohexanecarboxamidoxime (compound No. 463 of Table 1)

NMR ($CDCl_3$)
7.11 (t, 1H), 5.41 (d, 1H), 4.83 (m, 1H), 4.56 (m, 3H), 4.39 (m, 1H), 3.94 (m, 1H), 3.46 (m, 1H), 3.02 (m,

2H), 2.39 (m, 1H), 2.10-1.20 (m, 20H), 1.22 (dd, 6H), 1.02-0.84 (m, 2H), 0.86 (t, 6H)
IR: 33346, 2962, 2930, 1653, 1541, 1448, 1271, 1113

Example 43

Trans-4-[(S)-N-((R)-2-t-butoxycarbonylamino-4-ethyl-hexanoyl) prolyl] aminomethylcyclohexanecarboxamidoxime (compound No. 466 of Table 1)

NMR ($CDCl_3$)
7.19 (t, 1H), 5.14 (d, 1H), 4.60 (d, 1H), 4.50 (s, 2H), 4.33 (m, 1H), 3.89 (m, 1H), 3.43 (m, 1H), 3.15 (m, 1H), 2.95 (m, 1H), 2.40 (m, 1H), 2.10-1.19 (m, 20H), 1.43 (s, 9H), 1.04-0.89 (m, 2H), 0.86 (t, 6H)
IR: 3346, 2964, 2930, 1649, 1541, 1448, 1367, 1280, 1251, 1168, 929

Example 44

Trans-4-[(S)-N-((R)-2-ethoxycarbonylamino-heptanoyl) prolyl] aminomethylcyclohexanecarboxamidoxime (compound No. 459 of Table 1)

NMR ($CDCl_3$)
7.08 (t, 1H), 5.60 (d, 1H), 4.58 (m, 3H), 4.35 (m, 1H), 4.07 (m, 2H), 3.92 (m, 1H), 3.48 (m, 1H), 3.06 (m, 2H), 2.40 (m, 1H), 2.04-1.32 (m, 20H), 1.24 (t, 3H), 0.89 (t, 3H), 0.98 (m, 2H)
IR: 3346, 2928, 1649, 1541, 1448, 1255, 1055, 927

Example 45

Trans-4-[(S)-N-((R)-N'-t-butoxycarbonylamino-methionyl) prolyl] aminomethylcyclohexanecarboxamidoxime (compound No. 468 of Table 1)

NMR ($CDCl_3$)
7.07 (m, 1H), 5.31 (d, 1H), 4.55 (m, 4H), 3.56 (m, 1H), 3.10 (m, 2H), 2.57 (t, 2H), 2.37 (m, 1H), 2.11 (s, 3H), 2.06-1.29 (m, 14H), 1.43 (s, 9H), 1.00 (m, 2H)
IR: 3354, 2928, 1647, 1541, 1448, 1367, 1251, 1167

Example 46

Trans-4-[(S)-N-((R)-2-hydroxy-4,4-dimethyl-pentanoyl) prolyl] aminomethylcyclohexanecarboxamidoxime (compound No. 454 of Table 1)

NMR ($CDCl_3$)
7.19 (t, 1H), 4.68 (s, 2H), 4.50 (d, 1H), 4.36 (t, 1H), 3.64 (t, 1H), 3.39 (m, 1H), 3.06 (m, 2H), 2.35 (m, 2H), 2.16-1.79 (m, 9H), 1.44 (d, 2H), 1.43-1.25 (m, 3H), 1.00-0.95 (m, 2H), 1.02 (s, 9H)
IR: 3337, 2944, 1653, 1620, 1566, 1448, 1386, 1248, 1087

Example 47

Trans-4-[(S)-N-((R)-2-ethoxycarbonylamino-4-ethyl-hexanoyl) prolyl] aminomethylcyclohexanecarboxamidoxime (compound No. 460 of Table 1)

NMR ($CDCl_3$)
7.07 (t, 1H), 5.53 (d, 1H), 4.56 (m, 3H), 4.40 (m, 1H), 4.11 (q, 2H), 3.96 (m, 1H), 3.45 (m, 1H), 3.05 (m, 2H), 2.36 (m, 1H), 2.09-1.77 (m, 10H), 1.61-1.21 (m, 8H), 1.24 (t, 3H), 1.02-0.83 (m, 2H), 0.86 (t, 6H)
IR: 3342, 2962, 2930, 1649, 1541, 1448, 1379, 1269, 1059, 929

Example 48

Trans-4-[(S)-N-[(R)-2-ethoxycarbonylamino-4,4-dimethylpentanoyl] prolyl] aminomethylcyclohexanecarboxamide O-methoxycarbonyloxime (compound No. 531 of Table 1)

To a solution of the compound (4.2 g, 8.9 mmol) obtained in Example 33 and triethylamine (1.9 ml, 13.3 mmol) in dichloromethane (100 ml), a solution of methyl chloroformate (1.0 g, 10 mmol) in dichloromethane (10 ml) is added at 0 °C. After stirring for 4 hours, the organic layer is washed once with an aqueous saturated sodium bicarbonate solution, water and saturated brine, successively. After drying over sodium sulfate, the solvent is evaporated and the residue is purified with silica gel column chromatography (ethyl acetate-methanol) to give 2.9 g of the titled compound (62%).

NMR ($CDCl_3$)

0.89-1.07 (m, 11H), 1.21-1.60 (m, 8H), 1.79-2.40 (m, 9H), 3.0-3.10 (m, 2H), 3.40-3.50 (m, 1H), 3.84 (s, 3H), 3.84-4.20 (m, 3H), 4.35-4.40 (m, 1H), 4.55 (d, 1H), 4.81 (br, 2H), 5.19 (d, 1H), 7.12 (t, 1H)

IR: 3345, 2953, 1763, 1699, 1645, 1541, 1443, 1256

According to the same procedures, the compounds shown in the following Examples were synthesized.

Example 49

4-[(S)-N-((R)-2-hydroxy-2-cyclohexylacetyl) prolyl]aminomethylbenzamide O-ethoxycarbonyloxime (compound No. 543 of Table 1)

NMR ($CDCl_3$)

7.56 (d, 2H), 7.47 (t, 1H), 7.22 (d, 2H), 5.35 (s, 2H), 4.53 (m, 2H), 4.37 (d, 2H), 4.30 (q, 2H), 4.07 (m, 1H), 3.64 (m, 1H), 3.47 (m, 1H), 3.39 (m, 1H), 2.35-1.17 (m, 15H), 1.35 (t, 3H)

IR: 3368, 2928, 1772, 1628, 1554, 1452, 1404, 1228, 1087, 856

Example 50

Trans-4-[(S)-N-((R)-2-hydroxy-4,4-dimethylpentanoyl) prolyl] aminomethylcyclohexanecarboxamide O-methoxycarbonyloxime (compound No. 534 of Table 1)

NMR ($CDCl_3$)

7.07 (t, 1H), 4.77 (s, 2H), 4.52 (d, 1H), 4.34 (m, 1H), 3.85 (s, 3H), 3.58 (t, 1H), 3.37 (m, 1H), 3.22 (d, 1H), 3.12-3.05 (m, 2H), 2.26-2.21 (m, 1H), 1.97-1.37 (m, 13H), 1.03 (s, 9H), 1.09-0.95 (m, 2H)

IR: 3346, 2953, 1763, 1643, 1442, 1257, 1089, 879

Example 51

Trans-4-[(S)-N-((R)-2-hydroxy-4,4-dimethylpentanoyl)prolyl] aminomethylcyclohexanecarboxamide O-ethoxycarbonyloxime (compound No. 556 of Table 1)

NMR ($CDCl_3$)

7.05 (t, 1H), 4.73 (s, 2H), 4.52 (d, 1H), 4.34 (t, 1H), 4.27 (q, 2H), 3.58 (m, 1H), 3.45 (m, 1H), 3.08 (m, 2H), 2.44 (m, 1H), 2.30-1.30 (m, 13H), 1.32 (t, 3H), 1.03 (s, 9H), 1.07-0.92 (m, 2H)

IR: 3373, 2953, 1759, 1641, 1450, 1369, 1248, 1093

Example 52

Trans-4-amino-[(S)-N-[(R)-N'-methanesulfonylphenyalanyl] prolyl] aminomethylcyclohexane (compound No. 776 of Table 1) L-tartrate.

(a) Trans-4-t-butyloxycarbonylamino-benzyloxycarbonylaminomethylcyclohexane

To a solution of trans-4-aminomethylcyclohexanecarboxylic acid (15.7 g, 100 mmol) and sodium hydroxide (4.0 g, 100 mmol) in water (30 ml), benzyloxycarbonyl chloride (15.6 ml, 110 mmol) and sodium hydroxide (4.4 g, 110 mmol) in water (30 ml) are added dropwise at 0 °C, simultaneously. After stirring for 4 hours, the mixture is extracted once with ether and 1N-hydrochloric acid is added to the aqueous layer until

the pH of the mixture indicates 2. Then, the precipitated white solid is collected and dried.

To a solution of the resulting compound (12.8 g, 50 mmol) in t-butanol (150 ml), triethylamine (8.3 ml, 60 mmol) and DPPA (13.7 g, 50 mmol) are added and heated at reflux for 8 hours. After the solvent is evaporated, water is added to the residue and the mixture is extracted with chloroform. The organic layer is washed once with an aqueous sodium carbonate (5%), once with an aqueous potassium hydrogensulfate (5%), twice with water and once with saturated brine, successively, and then dried over sodium sulfate. The solvent is evaporated and the residue is purified with silica gel column chromatography (hexane-ethyl acetate) to give 8.6 g of the titled compound (47%).

NMR ($CDCl_3$)

0.85-1.37 (m, 14H), 1.60-1.85 (m, 4H), 2.84 (t, 1H), 3.12 (br, 1H), 5.00 (s, 2H), 6.62 (d, 1H), 7.23-7.39 (m, 6H)

(b) Trans-4-t-butyloxycarbonylamino-[(S)-N-benzyloxycarbonylprolyl] aminomethylcyclohexane

The compound (4.4 g, 12 mmol) obtained in the item (a) is dissolved in methanol (200 ml) and the catalytic hydrogenation is conducted at room temperature and under atomospheric pressure in the presence of palladium black (0.4 g). After the completion of the reaction, the catalyst is filtered off and the solvent is evaporated.

To a solution of (S)-Z-proline (3.0 g, 12 mmol) in THF (30 ml), CDI (2.0 g, 12 mmol) is added at 0 °C. After stirring for 3 hours, a solution of the compound obtained in the above reaction in THF (150 ml) is added at 0 °C. After stirring for 6 hours, the solvent is evaporated and water (50 ml) is added to the residue. The mixture is extracted with chloroform and the organic layer is washed three times with water and once with saturated brine, successively. After drying over sodium sulfate, the solvent is evaporated and the residue is purified with silica gel chromatography (chloroform-methanol) to give 4.2 g of the titled compound (77%).

NMR ($CDCl_3$)

0.85-1.06 (m, 4H), 1.44 (s, 9H), 1.60-2.35 (m, 9H), 2.94-3.20 (m, 2H), 3.20-3.55 (m, 3H), 4.31 (br, 1H), 4.47 (br, 1H), 5.14 (s, 2H), 6.90 (br, 1H), 7.15-7.40 (m, 5H)

(c) Trans-4-t-butyloxycarbonylamino-[(S)-N-[(R)-N'-benzyloxycarbonylphenylalanyl] prolyl] aminomethylcyclohexane

The compound (3.6 g, 7.9 mmol) obtained in the item (b) is dissolved in methanol (50 ml) and the catalytichydrogenation is conducted at room temperature and under atomospheric pressure in the presence of palladium black (0.3 g). After the completion of the reaction, the catalyst is filtered off and the solvent is evaporated.

To a solution of (R)-Z-phenylalanine (2.4 g, 7.9 mmol) in THF (30 ml), CDI (1.3 g, 7.9 mmol) is added at 0 °C. After stirring for 4 hours, a solution of the compound obtained in the above reaction in THF (60 ml) is added. After stirring for 8 hours, the solvent is evaporated and water is added to the reaction mixture. The mexture is extracted with chloroform and the organic layer is washed three times with water and once with saturated brine, successively, and then dried over sodium sulfate. The solvent is evaporated and the residue is purified with silica gel column chromatography (chloroform-methanol) to give 4.2 g of the titled compound (89%).

NMR ($CDCl_3$)

0.85-1.06 (m, 5H), 1.33-2.0 (m, 15H), 2.10-2.22 (m, 1H), 2.50-2.60 (m, 1H), 2.94-3.01 (m, 5H), 3.30 (br, 1H), 3.57 (t, 1H), 4.32-4.59 (m, 3H), 5.08 (d, 2H), 5.69 (d, 1H), 7.02 (br, 1H), 7.18-7.37 (m, 10H)

(d) Trans-4-amino-[(S)-N-[(R)-N'-methanesulfonylphenylalanyl]prolyl] aminomethylcyclohexane L-tartrate.

The compound (2.4 g, 3.9 mmol) obtained in the item (c) is dissolved in methanol (40 ml) and the catalytic hydrogenation is conducted at room temperature and under atomospheric pressure in the presence of palladium black (0.2 g). After the completion of the reaction, the catalyst is filtered off and the solvent is evaporated. To a solution of the resulting compound in dichloromethane (40 ml), triethylamine (0.65 ml, 4.7 mmol) is added and a solution of methanesulfonyl chloride (0.47 g, 4.1 mmol) in dichloromethane (100 ml) is further added at 0 °C. After stirring for 3 hours, an aqueous saturated sodium bicarbonate solution is added and the organic layer is washed once with water and saturated brine, successively. After drying over sodium sulfate, the solvent is evaporated and the residue is purified with silica gel chromatography (chloroform-methanol).

The resulting compound is dissolved in chloroform (10 ml) and a 4N-dioxane hydrochloride in dioxane (10 ml) is added at 0 °C. After stirring for 2 hours, the solvent is evaporated and chloroform (10 ml) and a 1N-sodium hydroxide solution (10 ml) are added to the residue and, further, the mixture is stirred for 10 minutes. The organic layer is dried over sodium sulfate and a solution of L-tartaric acid (0.34 g, 2.26 nm) in methanol (5 ml) is added.

The solvent is evaporated and ether (20 ml) is added, and then the precipitated white solid is collected and dried to give 1.36 g of the titled compound (58%).

NMR (DMSO-d^6)

7.77 (m, 4H), 7.28 (m, 5H), 4.28 (m, 1H), 4.16 (m, 1H), 3.57-3.45 (m, 8H), 2.73 (s, 3H), 1.91-1.75 (m, 9H), 1.54 (m, 1H), 1.25 (m, 4H), 0.93 (m, 2H)

IR: 3324, 2934, 1734, 1638, 1545, 1453, 1308, 1148

According to the same procedures, the compounds shown in the following Examples were synthesized.

Example 53

Trans-4-amino-[(S)-N-[(R)-2-methylsulfonylamino-2-cyclohexylacetyl] prolyl]aminomethylcyclohexane (compound No. 759 of Table 1) hydrochloride

NMR (DMSO-d^6)

8.09 (br, 3H), 7.80 (t, 1H), 7.39 (d, 1H), 4.30-4.26 (m, 1H), 3.87 (t, 1H), 3.80-3.45 (m, 2H), 3.0-2.80 (m, 3H), 2.85 (s, 3H), 2.10-0.80 (m, 24H)

IR: 3382, 2930, 2857, 1638, 1543, 1451, 1154

Example 54

Trans-4-amino-[(S)-N-[(S)-N'-benzenesulfonyl-α-glutamyl] prolyl] aminomethylcyclohexane (compound No. 792 of Table 1) hydrochloride

NMR (DMSO-d^6)

8.04 (br, 3H), 7.75-7.50 (m, 5H), 4.05 (q, 1H), 3.77-3.30 (m, 5H), 3.0-2.70 (m, 3H), 2.28 (t, 2H), 2.0-1.52 (m, 10H), 1.31-1.11 (m, 3H), 1.0-0.85 (m, 2H)

IR: 3400, 2937, 1637, 1449, 1161

Example 55

Trans-4-amino-[(S)-N-((RS)-3-methylsulfonylamino-3-phenylpropanoyl) prolyl]aminomethylcyclohexane (compound No. 777 of Table 1) hydrochloride

NMR (DMSO-d^6)

8.08 (m, 3H), 7.34 (m, 5H), 4.78 (m, 1H), 4.15 (m, 2H), 3.51 (m, 1H), 3.36 (m, 2H), 2.86 (m, 4H), 2.68 (s, 3H), 2.51 (m, 2H), 2.00-1.69 (m, 6H), 1.27 (m, 4H), 0.92 (m, 2H)

IR: 3409, 2936, 1638, 1453, 1314, 1148

Example 56

Trans-4-amino-[(S)-N-((R)-2-isopropoxycarbonylamino-4,4-dimethylpentanoyl) prolyl]-aminomethylcyclohexane (compound No. 797 of Table 1)

NMR ($CDCl_3$)

7.19 (m, 1H), 5.32 (d, 1H), 4.82 (m, 1H), 4.53 (m, 2H), 4.00 (m, 1H), 3.48 (m, 1H), 3.03-2.16 (m, 6H), 2.00-1.81 (m, 6H), 1.57 (d, 2H), 1.49 (m, 4H), 1.24 (m, 6H), 1.00 (s, 9H), 0.95 (m, 2H)

IR: 3326, 2949, 1640, 1541, 1449, 1248

Example 57

Trans-4-amino-[(S)-N-((R)-N'-ethoxycarbonyl-phenylalanyl) prolyl] aminomethylcyclohexane (compound No. 780 of Table 1) hydrochloride

NMR (DMSO-d^6)
7.98 (m, 3H), 7.37 (t, 1H), 7.26 (m, 5H), 4.37 (dd, 1H), 4.16 (m, 1H), 4.02 (m, 2H), 3.88 (m, 1H), 3.59 (m, 1H), 3.43 (m, 1H), 2.86 (m, 5H), 1.93-1.75 (m, 7H), 1.28 (m, 4H), 1.15 (t, 3H), 0.92 (m, 2H)
IR: 3349, 2936, 1642, 1537, 1451, 1258

Example 58

Trans-4-amino-[(S)-((R)-phenylalanyl) prolyl]aminomethylcyclohexane (compound No. 779 of Table 1) hydrochloride

NMR (DMSO-d^6)
8.69 (br, 3H), 8.09 (br, 4H), 7.37-7.20 (m, 5H), 4.19 (br, 1H), 4.09-4.06 (m, 1H), 3.20-2.82 (m, 5H), 2.0-0.85 (m, 15H)
IR: 3426, 2936, 1649, 1539, 1497, 1454

Example 59

Trans-4-amino-[(S)-N-((R)-2-ethoxycarbonyloxy-3-phenylpropanoyl) prolyl]aminomethylcyclohexane (compound No. 785 of Table 1) hydrochloride

NMR (DMSO-d^6)
7.78 (m, 3H), 7.30 (m, 5H), 7.15 (d, 1H), 5.22 (t, 1H), 4.20 (m, 1H), 4.08 (m, 3H), 3.64 (m, 1H), 3.02-2.88 (m, 5H), 1.92-1.72 (m, 7H), 1.20-0.94 (m, 9H)
IR: 3397, 2938, 1740, 1655, 1453, 1269

Example 60

Trans-4-amino-[(S)-N-((R)-2-allylcarbamoyloxy-3-phenylpropanoyl) prolyl]aminomethylcyclohexane (compound No. 787 of Table 1) hydrobromide

NMR (DMSO-d^6)
7.90 (m, 3H), 7.30 (m, 5H), 7.14 (m, 1H), 5.72 (m, 2H), 5.06 (m, 2H), 4.76 (m, 1H), 4.17 (m, 1H), 3.60 (m, 1H), 2.98-2.85 (m, 5H), 1.87-1.70 (m, 7H), 1.23 (m, 7H), 0.90 (m, 2H)
IR: 3364, 2936, 1707, 1645, 1543, 1454, 1256

Example 61

Trans-4-amino-[(S)-N-((R)-2-hydroxy-2-cyclohexylacetyl) prolyl] aminomethylcyclohexane (compound No. 768 of Table 1) hydrochloride

NMR (DMSO-d^6)
8.21 (br, 3H), 7.95 (m, 1H), 4.53 (m, 1H), 4.18 (d, 1H), 3.95 (m, 1H), 3.07 (m, 3H), 2.18-1.55 (m, 22H), 1.30-1.03 (m, 2H)
IR: 3422, 2928, 2854, 1637, 1450, 1388, 1240, 1114, 1045

Example 62

Trans-4-amino-[(S)-N-((R)-2-hydroxy-2-phenylacetyl) prolyl] aminomethylcyclohexane (compound No. 783 of Table 1) hydrochloride

NMR (DMSO-d^6)
7.98 (br, 3H), 7.37-7.28 (m, 5H), 5.48 (br, 1H), 5.23 (d, 1H), 4.23 (d, 1H), 3.70-3.35 (m, 2H), 3.0-2.80 (m, 4H), 2.0-1.60 (m, 8H), 1.40-0.90 (m, 5H)

IR: 3329, 2935, 1667, 1626, 1552, 1448

Example 63

Trans-4-amino-[(RS)-1-((R)-N'-methylsulfonyl-phenylalanyl)-2-piperidinecarboxyl]aminomethylcyclohexane (compound No. 834 of Table 1) hydrochloride

NMR (DMSO-d^6)
8.07 (m, 3H), 7.28 (m, 5H), 4.64 (m, 1H), 4.39 (m, 1H), 3.99 (m, 1H), 3.67 (m, 1H), 2.87 (m, 7H), 2.84 (s, 3H), 1.91-1.68 (m, 5H), 1.33-0.92 (m, 10H)
IR: 3385, 2936, 1638, 1535, 1453, 1314, 1150

Example 64

Trans-4-amino-[(S)-N-[(R)-2-ethoxycarbonylamino-4,4-dimethylpentanoyl] prolyl]aminomethylcyclohexane (compound No. 794 of Table 1)

NMR ($CDCl_3$)
7.16 (m, 1H), 5.68 (d, 1H), 4.53 (d, 1H), 4.38 (m, 1H), 4.10 (q, 2H), 4.01 (m, 1H), 3.46-3.07 (m, 4H), 2.30-1.81 (m, 8H), 1.58 (m, 5H), 1.26 (t, 3H), 1.00 (s, 9H), 0.95 (m, 2H)
IR: 3329, 2949, 1642, 1541, 1447, 1248, 1059

Example 65

Trans-4-(5-methyl-1,3-dioxo-2-on-4-ylmethyl)amino-[(S)-N-[(R)-2-ethoxycarbonylamino-4,4-dimethylpentanoyl] prolyl]aminomethylcyclohexane (compound No. 968 of Table 1)

To a solution of the compound (5.4 g, 11.7 mmol) obtained in Example 64 in DMF (40 ml), sodium carbonate (3.2 g, 23.4 mmol) is added, and a solution of 4-bromomethyl-5-methyl-1,3-dioxo-2-on (4.0 g, 17.6 mmol) in DMF (5 ml) is further added at 0 °C. After stirring for 48 hours, the solvent is evaporated and water is added to the residue, which is extracted with ethyl acetate. The organic layer is washed three times with water and once with saturated brine, successively, and then dried over sodium sulfate. The solvent is evaporated and the residue is purified with silica gel column chromatography (chloroform-methanol) to give 2.8 g of the titled compound (44%).
NMR ($CDCl_3$)
7.07 (m, 1H), 5.15 (d, 1H), 4.56 (d, 1H), 4.41 (m, 1H), 4.10 (q, 2H), 4.00 (m, 2H), 3.48 (s, 2H), 3.45 (m, 2H), 3.04 (t, 1H), 2.62 (m, 1H), 2.38 (m, 1H), 2.11 (s, 3H), 2.00 (m, 3H), 1.82 (m, 2H), 1.73-1.43 (m, 4H), 1.28 (t, 3H), 1.26 (m, 3H), 1.00 (s, 9H), 0.96 (m, 2H)
IR: 3329, 2934, 2870, 1823, 1649, 1539, 1445, 1223

According to the same procedures, the compounds shown in the following Examples were synthesized.

Example 66

Trans-4-t-butoxycarbonylamino-[(S)-N-[(R)-N'-methanesulfonylphenylalanyl] prolyl]aminomethylcyclohexane (compound No. 955 of Table 1)

NMR ($CDCl_3$)
7.29 (m, 3H), 7.24 (m, 2H), 6.67 (t, 1H), 5.61 (d, 1H), 4.40 (m, 2H), 4.29 (dd, 1H), 3.58 (m, 1H), 3.34 (m, 1H), 2.99 (m, 4H), 2.82 (s, 3H), 2.69 (m, 1H), 2.18-1.74 (m, 9H), 1.43 (s, 9H), 1.02 (m, 4H)
IR: 3376, 2932, 1655, 1526, 1453, 1322

Example 67

Trans-4-guanidino-[(S)-N-[(R)-N'-methanesulfonylphenylalanyl] prolyl]aminomethylcyclohexane (compound No. 646 of Table 1) sulfate

To a solution of the compound (0.45 g, 1 mmol) obtained in Example 52 in ethanol (15 ml), a solution of 2-methylisothiourea sulfate (0.14 g, 0.5 mmol) in water (5 ml) is added and heated at reflux for 6 hours. The

solvent is evaporated and ether (20 ml) is added. The precipitated white solid is collected and washed with ether, and then dried under reduced pressure to give 0.44 g of the titled compound (81%).
NMR (DMSO-d^6)
8.04-2.0 (m, 13H), 2.60-3.96 (m, 7H), 2.77 (s, 3H), 4.14-4.28 (m, 2H), 5.47 (br, 1H), 6.75 (br, 1H), 7.20-7.36 (m, 5H), 7.83 (br, 1H), 8.40 (br, 4H)
IR: 3322, 2932, 2193, 2153, 1644, 1545, 1451, 1319, 1150

According to the same procedure as that described in Example 1, the following compounds of Examples 68 to 78 were synthesized.

Example 68

4-Amidino-[(S)-N-[(R)-2-hydroxy-cyclohexylacetyl] prolyl] aminomethylbenzene (compound No. 82 of Table 1) hydrochloride

NMR (DMSO-d^6)
9.29 (br, 2H), 8.93 (br, 2H), 8.51 (t, 1H), 7.75 (d, 2H), 7.49 (d, 2H), 4.37 (m, 3H), 3.96 (d, 1H), 3.70 (m, 1H), 3.60-3.40 (m, 2H) 2.20-1.0 (m, 14H)
IR: 3227, 2922, 1657, 1607, 1539, 1485, 1458, 1323, 1246, 1032

Example 70

4-Amidino-[(S)-N-[(R)-2-methylsulfonylamino-3,3-dimethylbutanoyl] prolyl]aminomethylbenzene (compound No. 114 of Table 1) hydrochloride

NMR (DMSO-d^6)
9.41 (br, 2H), 9.24 (br, 2H), 8.63 (t, 1H), 7.81 (d, 2H), 7.47 (d, 2H), 7.20 (d, 1H), 4.42 (dd, 1H), 4.35 (t, 2H), 3.96 (d, 1H), 3.80-3.60 (m, 2H), 2.85 (s, 3H), 2.20-1.80 (m, 4H), 0.97 (s, 9H)
IR: 3273, 2970, 2365, 1630, 1541, 1483, 1412, 1304, 1153, 715

Example 70

4-Amidino-[(S)-N-[(R)-2-methylsulfonylamino-6-ethoxycarbonylhexanoyl] prolyl]aminomethylbenzene (compound No. 117 of Table 1) hydrochloride

NMR (DMSO-d^6)
9.35 (br, 4H), 8.66 (t, 1H), 7.79 (d, 1H), 7.48 (d, 2H), 4.35 (m, 3H), 4.65 (q, 2H), 3.69 (m, 1H), 3.55 (m, 1H), 2.75 (s, 3H), 2.29 (t, 2H), 2.13 (m, 2H), 1.94 (m, 2H), 1.85 (m, 2H), 1.52 (m, 7H), 1.18 (t, 3H)
IR: 3382, 1644, 1547, 1427, 1375, 1314, 1150, 1111

Example 71

4-Amidino-[(S)-N-[(R)-2-methylsulfonylamino-4-(3'-carboxy)-phenylbutanoyl] prolyl]aminomethylbenzene (compound No. 119 of Table 1) hydrochloride

NMR (DMSO-d^6)
9.45 (s, 2H), 9.38 (s, 2H), 8.62 (t, 1H), 7.84 (m, 2H), 7.79 (d, 2H), 7.64 (d, 1H), 7.47 (d, 2H), 7.42 (m, 2H), 4.33 (m, 3H), 4.10 (m, 1H), 3.57-3.37 (m, 2H), 2.85 (m, 1H), 2.78 (s, 3H), 2.73 (m, 1H), 2.12 (m, 1H), 1.95-1.81 (m, 6H)
IR: 3366, 1638, 1543, 1489, 1449, 1311, 1150, 754, 527

Example 72

4-Amidino-[(S)-N-[(R)-N'-methylsulfonyl-O-(4'-carboxyphenyl)-seryl] prolyl]aminomethylbenzene (compound No. 970 of Table 1) hydrochloride

NMR (DMSO-d^6)
9.31 (s, 2H), 9.00 (s, 2H), 8.59 (t, 1H), 7.90 (d, 2H), 7.83 (d, 1H), 7.75 (d, 2H), 7.48 (d, 2H), 7.03 (d, 2H), 4.35 (m, 4H), 4.22 (m, 2H), 4.12 (dd, 1H), 3.72 (m, 2H), 2.89 (s, 3H), 2.20-1.80 (m, 4H)

IR: 3376, 1647, 1607, 1424, 1318, 1252, 1154, 1119, 774, 633, 525

Example 73

4-Amidino-[(S)-N-[(R)-N'-methylsulfonyl-O-ethoxycarbonylmethyl-tyrosyl] prolyl]aminomethylbenzene (compound No. 971 of Table 1) hydrochloride

NMR (DMSO-d^6)
9.41 (br, 2H), 9.20 (br, 2H), 8.56 (t, 1H), 7.80 (d, 2H), 7.65 (d, 1H), 7.48 (d, 2H), 7.18 (dd, 2H), 6.84 (dd, 2H), 4.75 (q, 1H), 4.30 (dd, 1H), 4.30-4.25 (m, 2H), 3.70-3,.42 (m, 3H), 3.47 (q, 2H), 3.18 (t, 1H), 2.83 (d, 2H), 2.72 (s, 3H), 1.89-1.60 (m, 4H), 1.14 (dt, 3H)
IR: 3370, 2365, 1742, 1636, 1541, 1512, 1445, 1308

Example 74

4-Amidino-[(S)-N-[(R)-N'-ethoxycarbonylphenylalanyl] prolyl] aminomethylbenzene (compound No. 972 of Table 1) hydrochloride

NMR (DMSO-d^6)
9.40 (br, 2H), 9.24 (br, 2H), 8.14 (t, 1H), 7.80 (d, 2H), 7.59 (t, 1H), 7.45 (d, 2H), 7.31-7.15 (m, 5H), 4.50-4.26 (m, 4H), 3.90-3.57 (m, 3H), 3.0-2.7 (m, 3H), 1.9-1.6 (m, 4H), 1.10-1.0 (m, 3H)
IR: 3279, 2364, 1637, 1539, 1491, 1450, 1255, 704

Example 75

4-Amidino-[(S)-N-[(R)-2-methylsulfonylaminoheptanoyl] prolyl] aminomethylbenzene (compound No. 973 of Table 1) hydrochloride

NMR (DMSO-d^6)
9.37 (s, 2H), 9.16 (s, 2H), 8.60 (t, 1H), 7.76 (d, 2H), 7.48 (d, 2H), 7.40 (d, 1H), 4.50-4.23 (m, 3H), 4.08 (m, 1H), 3.69 (m, 1H), 3.36 (m, 1H), 2.74 (s, 3H), 2.15 (m, 1H), 2.09-1.84 (m, 3H), 1.61-1.22 (m, 8H), 0.87 (m, 3H)
IR: 3366, 2957, 1638, 1543, 1489, 1426, 1314, 1154, 718, 527

Example 76

4-Amidino-[(S)-N-[(R)-N'-methylsulfonyl-O-(3'-carboxymethyl-phenyl)-seryl] prolyl]aminomethylbenzene (compound No. 974 of Table 1) hydrochloride

NMR (DMSO-d^6)
9.46 (s, 2H), 9.31 (s, 2H), 8.70 (t, 1H), 7.83 (m, 3H), 7.48 (d, 2H), 7.19 (m, 2H), 6.89 (d, 2H), 4.58 (dd, 1H), 4.37 (m, 4H), 4.14 (d, 2H), 3.70 (m, 1H), 3.60 (m, 3H), 2.89 (s, 3H), 2.11 (m, 1H), 2.01-1.82 (m, 3H)
IR: 3382, 1724, 1640, 1543, 1489, 1447, 1316, 1262, 1154, 768, 527

Example 77

4-Amidino-[(S)-N-[(R)-N'-methylsulfonyl-O-(4'-carboxymethyl-phenyl)-seryl] prolyl]aminomethylbenzene (compound No. 975 of Table 1) hydrochloride

NMR (DMSO-d^6)
9.45 (s, 2H), 9.29 (s, 2H), 8.70 (t, 1H), 7.83 (d, 2H), 7.82 (d, 2H), 7.48 (d, 2H), 7.24 (d, 1H), 6.82 (d, 2H), 4.59 (dd, 1H), 4.37 (m, 4H), 4.14 (d, 2H), 3.70 (m, 1H), 3.61 (m, 3H), 2.89 (s, 3H), 2.11 (m, 1H), 2.01-1.82 (m, 3H)
IR: 3383, 1640, 1545, 1514, 1437, 1312, 1242, 1152, 824, 523

Example 78

4-Amidino-[(S)-N-[(R)-2-ethoxycarbonylmethylsulfonylamino-heptanoyl] prolyl]aminomethylbenzene (compound No. 976 of Table 1) hydrochloride

NMR (DMSO-d^6)
9.36 (s, 2H), 9.15 (s, 2H), 8.49 (t, 1H), 7.81 (d, 1H), 7.77 (d, 2H), 7.47 (d, 2H), 4.35 (m, 3H), 4.21 (d, 1H), 4.15 (m, 1H), 4.06 (q, 2H), 3.93 (d, 1H), 3.73 (m, 1H), 3.53 (m, 1H), 2.14 (m, 1H), 1.94 (m, 3H), 1.67-1.18 (m, 8H), 1.14 (t, 3H), 0.89 (m, 3H)
IR: 3274, 2957, 2872, 1821, 1738, 1647, 1541, 1422, 1319, 1159, 1022, 723, 628, 527

According to the same procedures as that described in Example 15, the following compounds of Examples 79 to 86 were synthesized.

Example 79

Trans-4-amidino-[(S)-N-[(R)-N'-ethoxycarbonyl-O-t-butyloxy-seryl]prolyl] aminomethylcyclohexane (compound No. 240 of Table 1) hydrochloride

NMR (DMSO-d^6)
8.88 (br, 2H), 8.71 (br, 2H), 7.72 (m, 1H), 6.39 (m, 1H), 4.59 (m, 1H), 4.52 (m, 1H), 4.11 (m, 2H), 3.86-3.71 (m, 2H), 3.58 (m, 2H), 3.22 (m, 2H), 2.79-0.88 (m, 15H), 1.24 (t, 3H), 1.15 (s, 9H)
IR: 3271, 2976, 1685, 1647, 1541, 1448, 1257, 1192, 1095, 1055

Example 80

Trans-4-amidino-[(S)-N-[(R)-N'-isopropoxycarbonyl-O-(1',1'-dimethylpropyl)-seryl] prolyl]-aminomethylcyclohexane (compound No. 977 of Table 1) hydrochloride

NMR (DMSO-d^6)
8.74 (br, 4H), 7.68 (m, 1H), 6.01 (m, 1H), 4.83 (m, 1H), 4.57 (m, 2H), 3.74 (m, 2H), 3.50 (m, 2H), 3.14 (m, 1H), 2.97 (m, 1H), 2.5-0.9 (m, 16H), 1.24 (dd, 6H), 1.09 (s, 6H), 0.81 (t, 3H)
IR: 3314, 2978, 1693, 1641, 1543, 1450, 1375, 1261, 1111, 1059

Example 81

Trans-4-amidino-[(S)-N-[(R)-N'-ethoxycarbonyl-O-(1',1'-dimethylpropyl)-seryl] prolyl]-aminomethylcyclohexane (compound No. 978 of Table 1) hydrochloride

NMR (DMSO-d^6)
8.75 (br, 4H), 7.55 (m, 1H), 6.40 (m, 1H), 4.52 (m, 2H), 4.13 (m, 2H), 3.88-3.70 (m, 2H), 3.55 (m, 2H), 3.28 (m, 1H), 2.87-2.70 (m, 1H), 2.20-1.20 (m, 14H), 1.27 (t, 3H), 1.09 (s, 6H), 0.81 (t, 3H), 1.10-0.90 (m, 2H)
IR: 3292, 2974, 1689, 1645, 1543, 1448, 1259, 1095, 1055

Example 82

Trans-4-amidino-[(S)-N-[(R)-N'-isopropoxycarbonyl-O-(1'-ethyl-1'-methyl-propyl)-seryl] prolyl]-aminomethylcyclohexane (compound No. 979 of Table 1) hydrochloride

NMR (DMSO-d^6)
8.78 (s, 2H), 8.69 (s, 2H), 7.55 (br, 1H), 5.99 (br, 1H), 4.84 (m, 1H), 4.54 (m, 2H), 3.71 (m, 2H), 3.49 (m, 2H), 3.20-0.90 (m, 16H), 1.64 (q, 4H), 1.23 (t, 6H), 1.03 (s, 3H), 0.78 (t, 6H)
IR: 3315, 2976, 2934, 1685, 1641, 1543, 1450, 1375, 1261, 1111

Example 83

Trans-4-amidino-[(S)-N-[(R)-N'-ethoxycarbonyl-S-t-butyl-cystinyl]prolyl] aminomethylcyclohexane (compound No. 980 of Table 1) hydrochloride

NMR (DMSO-d^6)
8.82 (br, 2H), 8.74 (br, 2H), 7.47 (m, 1H), 6.63 (m, 1H), 4.60-4.40 (m, 2H), 4.20-4.21 (m, 2H), 4.00 (m, 1H), 3.72 (m, 1H), 3.24 (m, 1H), 2.87 (m, 2H), 2.65 (m, 1H), 2.18-1.31 (m, 12H), 1.31 (s, 9H), 1.27 (t, 3H), 1.10-0.90 (m, 2H)
IR: 3298, 2932, 1693, 1641, 1541, 1448, 1304, 1257, 1161, 1047

Example 84

Trans-4-amidino-[(S)-N-[(R)-N'-isopropoxycarbonyl-0-(1'-methylcyclopentyl)-seryl] prolyl]-aminomethylcyclohexane (compound No. 981 of Table 1) hydrochloride

NMR (DMSO-d^6)
8.79 (br, 4H), 7.64 (m, 1H), 5.97 (m, 1H), 4.83 (m, 1H), 4.55 (m, 2H), 3.76 (m, 2H), 3.52 (m, 2H), 3.15-1.20 (m, 22H), 1.27-1.13 (m, 9H), 1.13-0.95 (m, 2H)
IR: 3329, 2934, 1684, 1639, 1541, 1450, 1261, 1182, 1111, 1060, 918

Example 85

Trans-4-amidino-[(S)-N-[(R)-N'-isopropoxycarbonyl-0-t-butyl-threonyl] prolyl]aminomethylcyclohexane (compound No. 982 of Table 1) hydrochloride

NMR (DMSO-d^6)
8.74 (m, 4H), 7.80 (m, 1H), 5.66 (m, 1H), 4.85 (m, 1H), 4.57 (m, 1H), 4.29 (m, 1H), 3.80-3.60 (m, 3H), 3.05 (m, 2H), 2.60 (m, 1H), 2.50-1.20 (m, 11H), 1.27-1.22 (m, 15H), 1.15 (d, 3H), 1.10-0.90 (m, 2H)
IR: 3331, 2978, 1697, 1639, 1543, 1450, 1375, 1265, 1182, 1111

Example 86

Trans-4-amidino-[(S)-N-[(R)-2-ethoxycarbonylamino-3-isopropylthio-3-methyl-butanoyl] prolyl]-aminomethylcyclohexane (compound No. 983 of Table 1) hydrochloride

NMR (DMSO-d^6)
9.13 (br, 2H), 8.46 (br, 2H), 7.30 (m, 1H), 5.85 (m, 1H), 4.55 (m, 1H), 4.36 (m, 1H), 4.15-3.85 (m, 3H), 3.69 (m, 1H), 3.02 (m, 2H), 2.30 (m, 1H), 2.00-1.20 (m, 13H), 1.48 (s, 3H), 1.33 (s, 3H), 1.30-1.20 (m, 9H), 1.05-0.85 (m, 2H)
IR: 3420, 2974, 1635, 1556, 1521, 1448, 1385, 1298, 1259, 1060

According to the same procedures as that described in Example 24, the following compounds of Examples 87 to 113were synthesized.

Example 87

4-[(S)-N-[(R)-2-hydroxy-cyclohexylacetyl] prolyl] aminomethylbenzamidoxime (compound No. 391 of Table 1)

NMR (DMSO-d^6)
9.55 (br, 1H), 8.31 (t, 1H), 7.59 (d, 2H), 7.24 (d, 2H), 5.73 (br, 2H), 4.57 (m, 1H), 4.26-4.32 (m, 3H), 3.91 (br, 1H), 3.40-3.60 (m, 2H), 2.05-0.80 (m, 15H)
IR: 3375, 2926, 2853, 1638, 1561, 1451, 1385, 1244

Example 88

4-[(S)-N-[(R)-N'-isopropoxycarbonyl-phenylalanyl] prolyl] aminomethylbenzamidoxime (compound No. 395 of Table 1)

NMR ($CDCl_3$)
7.65 (br, 1H), 7.53 (d, 2H), 7.29-7.19 (m, 8H), 5.89 (d, 2H), 5.01 (br, 2H), 4.58-4.45 (m, 4H), 4.27 (dd, 1H), 3.65 (br, 1H), 3.10-2.93 (m, 2H), 2.58 (q, 1H), 2.17 (br, 1H), 1.90-1.50 (m, 2H), 1.11 (d, 4H), 0.96 (d, 2H)
IR: 3331, 2980, 2880, 2365, 1639, 1539, 1452, 126

Example 89

4-[(S)-N-[(R)-2-ethoxycarbonylamino-phenylacetyl] prolyl] aminomethylbenzamidoxime (compound No. 403 of Table 1)

NMR ($CDCl_3$)
7.80 (br, 1H), 7.47 (d, 2H), 7.40-7.14 (m, 8H), 6.11 (dd, 1H), 5.43 (dd, 1H), 4.98 (br, 2H), 4.70-4.54 (m, 2H), 4.50-4.20 (m, 1H), 4.15-4.00 (m, 1H), 4.00-3.80 (m, 2H), 3.25-3.19 (m, 1H), 2.30-1.80 (m, 4H), 1.16 (dt, 3H)
IR: 3339, 2980, 2365, 1641, 1524, 1437, 1385, 1057

Example 90

4-[(S)-N-[(R)-N'-ethoxycarbonyl-valyl]prolyl] aminomethylbenzamidoxime (compound No. 407 of Table 1)

NMR ($CDCl_3$)
7.57 (br, 1H), 7.54 (d, 2H), 7.20 (d, 2H), 5.98 (d, 1H), 4.97 (br, 2H), 4.68-4.59 (m, 2H), 4.24 (dd, 1H), 4.07 (t, 1H), 4.10-4.00 (m, 1H), 3.90-3.80 (m, 1H), 3.60-3.45 (m, 2H), 2.31 (br, 1H), 2.20-1.95 (m, 4H) 1.88 (d, 1H), 1.01 (t, 3H), 0.97 (d, 6H)
IR: 3337, 2971, 2878, 2363, 1640, 1539, 1445, 1277, 1238

Example 91

4-[(S)-N-[(R)-2-ethoxycarbonylamino-3,3-dimethylbutanoyl] prolyl] aminomethylbenzamidoxime (compound No. 409 of Table 1)

NMR ($DMSO\text{-}d^6$)
8.01 (br, 1H), 7.59 (d, 2H), 7.21 (d, 2H), 7.19-7.15 (m, 1H), 5.73 (br, 2H), 4.36-4.24 (m, 4H), 4.0-3.60 (m, 4H), 2.10-1.80 (m, 5H), 1.06 (t, 3H), 0.96 (s, 9H)
IR: 3345, 2966, 2364, 1647, 1535, 1443, 1240

Example 92

4-[(S)-N-[(R)-2-ethoxycarbonylamino-heptanoyl) prolyl] aminomethylbenzamidoxime (compound No. 411 of Table 1)

NMR ($CDCl_3$)
7.63 (m, 1H), 7.51 (d, 2H), 7.20 (d, 2H), 5.85 (d, 2H), 4.99 (br, 1H), 4.67-4.58 (m, 2H), 4.35-4.28 (m, 2H), 3.99 (br, 1H), 3.86-3.80 (m, 1H), 3.58-3.50 (m, 2H), 2.31 (br, 1H), 2.07-1.90 (m, 3H), 1.80-1.50 (m, 2H), 1.40-1.10 (m, 5H), 1.03 (t, 3H), 1.01-0.84 (m, 3H)
IR: 3347, 2961, 2363, 2342, 1641, 1541, 1447, 1263, 1049

Example 93

4-[(S)-N-[(R)-2-t-butyloxycarbonylamino-heptanoyl] prolyl] aminomethylbenzamidoxime (compound No. 412 of Table 1)

NMR ($CDCl_3$)
7.74-7.70 (m, 1H), 7.49 (d, 2H), 7.27 (t, 1H), 7.20 (d, 2H), 5.43 (d, 1H), 4.93 (br, 2H), 4.65 (d, 1H), 4.48-4.25 (m, 3H), 3.93 (br, 1H), 3.50 (q, 1H), 2.40-2.30 (m, 1H), 2.10-1.90 (m, 3H), 1.70-1.50 (m, 2H), 1.42-1.21 (m, 13H), 0.92-0.80 (m, 3H)
IR: 3337, 2961, 2934, 2363, 1641, 1535, 1449, 1368, 1165

Example 94

4-[(S)-N-[(R)-2-ethoxycarbonylamino-4,4-dimethylpentanoyl] prolyl] aminomethylbenzamidoxime (compound No. 418 of Table 1)

NMR ($CDCl_3$)
7.58-7.51 (m, 1H), 7.53 (d, 2H), 7.20 (d, 2H), 5.87 (d, 1H), 5.01 (br, 2H), 4.64-4.56 (m, 2H), 4.40 (q, 1H), 4.26 (dd, 1H), 4.10-4.00 (m, 1H), 3.84-3.78 (m, 1H), 3.53-3.47 (m, 2H), 2.32 (br, 1H), 2.10-1.90 (m, 3H), 1.61 (d, 2H), 1.00 (t, 3H), 0.97 (s, 9H)
IR: 3324, 2957, 2263, 2342, 1642, 1541, 1445, 1248, 1059

Example 95

4-[(S)-N-[(R)-N'-(ethoxycarbonylmethyl)oxycarbonyl-phenylalanyl] prolyl]aminomethylbenzamidoxime (compound No. 984 of Table 1)

NMR ($CDCl_3$)
7.54 (d, 2H), 7.41 (br, 1H), 7.28-7.20 (m, 8H), 6.70 (d, 1H), 5.09 (br, 2H), 4.66 (dd, 1H), 4.60-4.55 (m, 2H), 4.22-4.00 (m, 4H), 4.03 (q, 2H), 3.62 (br, 1H), 3.10-3.02 (m, 2H), 2.60-2.40 (m, 1H), 2.14 (br, 1H), 2.00-1.50 (m, 3H), 1.22 (t, 3H)
IR: 3356, 3063, 2980, 2364, 1717, 1641, 1539, 1451, 1213, 702

Example 96

4-[(S)-N-[(R)-2-ethoxycarbonylamino-cyclohexylacetyl] prolyl] aminomethylbenzamidoxime (compound No. 985 of Table 1)

NMR ($CDCl_3$)
7.52 (d, 2H), 7.54-7.50 (m, 1H), 7.20 (d, 2H), 6.03 (br, 1H), 4.97 (br, 2H), 4.68 (q, 2H), 4.22 (dd, 1H), 4.12-4.03 (m, 2H), 3.64-3.47 (m, 1H), 3.20 (s, 3H), 2.32 (br, 1H), 2.05-1.60 (m, 9H), 1.28-0.97 (m, 6H)
IR: 3343, 2928, 2853, 2365, 1639, 1541, 1449, 1260

Example 97

4-[(S)-N-[(R)-2-ethoxycarbonylamino-2'-thienylacetyl] prolyl] aminomethylbenzamidoxime (compound No. 986 of Table 1)

NMR ($CDCl_3$)
7.80-7.60 (m, 1H), 7.46 (dd, 2H), 7.40-6.95 (m, 5H), 6.13 (dd, 1H), 5.71 (dd, 1H), 4.99 (br, 2H), 4.75-4.20 (m, 3H), 4.00-3.80 (m, 2H), 3.70-3.50 (m, 1H), 3.40-3.30 (m, 1H), 2.40-1.80 (m, 4H), 1.16 (dt, 3H)
IR: 3337, 2978, 2364, 1641, 1524, 1443, 1240, 1057, 710

Example 98

4-[(S)-N-[(R)-2-ethoxycarbonylamino-4'-fluorophenylacetyl] prolyl] aminomethylbenzamidoxime (compound No. 987 of Table 1)

NMR ($CDCl_3$)
7.80 (t, 1H), 7.46-7.27 (m, 4H), 7.19-6.92 (m, 4H), 6.19-6.15 (m, 1H), 5.50 (dd, 1H), 5.02 (br, 2H), 4.70-4.20 (m, 3H), 4.10-3.70 (m, 4H), 3.22-3.15 (m, 1H), 2.25-1.80 (m, 4H), 1.16 (dt, 3H)
IR: 3345, 3073, 2980, 2363, 2344, 1641, 1510, 1143

Example 99

4-[(S)-N-[(R)-N'-benzyloxycarbonyl-phenylalanyl] prolyl] aminomethylbenzamidoxime (compound No. 988 of Table 1)

NMR ($CDCl_3$)
7.50 (d, 2H), 7.49-7.30 (m, 1H), 7.26-7.12 (m, 12H), 6.40-6.10 (m, 1H), 4.85 (br, 2H), 4.90-4.70 (m, 1H), 4.55-4.40 (m, 4H), 4.30-4.20 (m, 1H), 3.70-3.60 (m, 1H), 3.03-2.95 (m, 1H), 2.20-2.15 (m, 1H), 2.00-1.45 (m, 3H)

Example 100

4-[(S)-N-(R)-2-t-butyloxycarbonylamino-4,4-dimethylpentanoyl] prolyl] aminomethylbenzamidoxime (compound No. 989 of Table 1)

NMR ($CDCl_3$)
7.67 (t, 1H), 7.53 (d, 2H), 7.22 (d, 2H), 5.34 (d, 1H), 4.91 (br, 2H), 4.65 (d, 1H), 4.42-4.34 (m, 3H), 4.00-3.90 (m, 1H), 3.48 (q, 1H), 2.40-2.30 (m, 1H), 2.02-1.95 (m, 3H), 1.56-1.53 (m, 2H), 1.31 (s, 9H), 0.98 (s, 9H)
IR: 3345, 2959, 2367, 1641, 1535, 1446, 1367, 1167

Example 101

4-[(S)-N-[(R)-N'-dimethylcarbamoyl-phenylalanyl] prolyl] aminomethylbenzamidoxime (compound No. 990 of Table 1)

NMR (DMSO-d^6)
9.56 (s, 1H), 8.11 (t, 1H), 7.56 (d, 2H), 7.18 (d, 2H), 7.29-7.16 (m, 5H), 6.70 (d, 1H), 5.74 (br, 2H), 4.40-4.05 (m, 4H), 2.94 (d, 2H), 2.93-2.70 (m, 2H), 2.60 (s, 6H), 1.90-1.60 (m, 4H)
IR: 3306, 2932, 2880, 2363, 2341, 1634, 1541, 1453

Example 102

4-[(S)-N-[(S)-N'-benzyloxycarbonyl-β-t-butylaspartyl] prolyl] aminomethylbenzamidoxime (compound No. 991 of Table 1)

NMR ($CDCl_3$)
7.63 (br, 1H), 7.51 (d, 2H), 7.33-7.26 (m, 5H), 7.18 (d, 2H), 6.07 (d, 1H), 5.08 (dd, 2H), 4.92 (br, 2H), 4.90-4.70 (m, 1H), 4.66 (d, 1H), 4.40 (d, 2H), 3.90-3.80 (m, 2H), 3.0-2.90 (m, 1H), 2.55 (dd, 1H), 2.35-2.20 (m, 1H), 2.08-1.90 (m, 3H), 1.25 (s, 9H)
IR: 3364, 3063, 2978, 2363, 2343, 2343, 1717, 1641, 1539, 1450, 1369, 1253, 1157

Example 103

Trans-4-[(S)-N-[(R)-N'-ethoxycarbonyl-O-t-butoxy-seryl] prolyl] aminomethylcyclohexanecarboxamidoxime (compound No. 485 of Table 1)

NMR ($CDCl_3$)
7.16 (m, 1H), 5.53 (m, 1H), 4.60-4.53 (m, 2H), 4.47 (s, 2H), 4.13-4.06 (m, 2H), 3.76 (br, 2H), 3.60-3.50 (m, 2H), 3.07 (br, 2H), 2.41 (m, 2H), 2.04-1.20 (m, 12H), 1.27 (t, 3H), 1.16 (s, 9H), 1.03-0.94 (m, 2H)
IR: 3352, 2930, 1701, 1651, 1541, 1448, 1259, 1053, 754

Example 104

Trans-4-[(S)-N-[(R)-N'-isopropoxycarbonyl-O-t-butylseryl] prolyl] aminomethylcyclohexanecarboxamidoxime (compound No. 486 of Table 1)

NMR ($CDCl_3$)
7.19 (m, 1H), 5.40 (d, 1H), 4.87 (m, 1H), 4.61-4..53 (m, 2H), 4.47 (br, 2H), 3.75 (m, 2H), 3.60-3.40 (m, 2H), 3.08 (t, 2H), 2.40 (m, 1H), 2.20-1.20 (m, 12H), 1.21 (dd, 6H), 1.19 (s, 9H), 1.10-0.90 (m, 2H)
IR: 3356, 2976, 1697, 1649, 1541, 1448, 1261, 1190, 1109, 1022

Example 105

Trans-4-[(S)-N-[(R)-N'-ethoxycarbonyl-O-t-(1',1'-dimethylpropyl]seryl)prolyl]-aminomethylcyclohexanecarboxamidoxime (compound No. 487 of Table 1)

NMR ($CDCl_3$)
7.14 (m, 1H), 5.51 (d, 1H), 4.60-4.50 (m, 2H), 4.48 (br, 2H), 4.09 (m, 2H), 3.78 (m, 2H), 3.55-3.45 (m, 2H), 3.06 (m, 2H), 2.35 (m, 1H), 2.20-0.90 (m, 16H), 1.24 (t, 3H), 1.10 (s, 6H), 0.82 (t, 3H)
IR: 3346, 2976, 2930, 1649, 1543, 1448, 1261, 1176, 1095, 1055

Example 106

Trans-4-[(S)-N-[(R)-N'-isopropoxycarbonyl-O-(1',1'-dimethylpropyl)-seryl] prolyl]-aminomethylcyclohexanecarboxamidoxime (compound No. 488 of Table 1)

NMR ($CDCl_3$)
7.18 (m, 1H), 5.38 (d, 1H), 4.86 (m, 1H), 4.61-4.50 (m, 2H), 4.47 (br, 2H), 3.77 (m, 2H), 3.57-3.42 (m, 2H), 3.06 (t, 2H), 2.39 (m, 1H), 2.20-0.90 (m, 16H), 1.23 (dd, 6H), 1.10 (s, 6H), 0.82 (t, 3H)
IR: 3346, 2976, 1703, 1651, 1541, 1448, 1263, 1178, 1109, 1030

Example 107

Trans-4-[(S)-N-[(R)-N'-isopropoxycarbonyl-O-(1'-ethyl-1'-methyl-propyl)-seryl] prolyl]-aminomethylcyclohexanecarboxamidoxime (compound No. 490 of Table 1)

NMR ($CDCl_3$)
7.17 (br, 1H), 5.35 (br, 1H), 4.86 (m, 1H), 4.60-4.50 (m, 2H), 4.47 (br, 2H), 3.78 (m, 2H), 3.53-3.38 (m, 2H), 3.07 (t, 2H), 2.37-1.20 (m, 17H), 1.23 (t, 6H), 1.06 (s, 3H), 1.06-0.82 (m, 2H), 0.79 (t, 6H)
IR: 3350, 2976, 2932, 1651, 1541, 1450, 1375, 1263, 1109, 1026

Example 108

Trans-4-[(S)-N-[(R)-N'-ethoxycarbonyl-S-t-butyl-cystinyl] prolyl] aminomethylcyclohexanecarboxamidoxime (compound No. 492 of Table 1)

NMR ($CDCl_3$)
7.27 (m, 1H), 5.81 (m, 1H), 4.60-4.40 (m, 2H), 4.88 (br, 2H), 4.11 (m, 2H), 3.87 (m, 1H), 3.68 (m, 1H), 3.06 (m, 2H), 2.90-2.70 (m, 2H), 2.37 (m, 1H), 2.10-1.20 (m, 12H), 1.32 (s, 9H), 1.25 (t, 3H), 1.10-0.90 (m,

2H)
IR: 3346, 2930, 1699, 1649, 1541, 1448, 1257, 1163, 1051, 929

Example 109

Trans-4-[(S)-N-[(R)-2-ethoxycarbonylamino-3-isopropylthio-3-methylbutanoyl] prolyl]-aminomethylcyclohexanecarboxamidoxime (compound No. 497 of Table 1)

NMR ($CDCl_3$)
7.16 (m, 1H), 5.62 (m, 1H), 4.61 (d, 1H), 4.47 (br, 2H), 4.35 (d, 1H), 4.12 (m, 2H), 3.96 (m, 1H), 3.76 (m, 1H), 3.10 (m, 1H), 3.00 (m, 2H), 2.38 (m, 1H), 2.00-1.20 (m, 12H), 1.47 (s, 3H), 1.40 (s, 3H), 1.33-1.25 (m, 9H), 1.00-0.90 (m, 2H)
IR: 3354, 2928, 1653, 1541, 1446, 1367, 1302, 1251, 1155, 1055

Example 110

Trans-4-[(S)-N-[(S)-N'-t-butyloxycarbonyl-seryl] prolyl] aminomethylcyclohexanecarboxamidoxime (compound No. 992 of Table 1)

NMR ($CDCl_3$)
7.76 (br, 1H), 6.10 (br, 1H), 5.40 (br, 1H), 4.60 (br, 4H), 3.96 (br, 4H), 3.16-1.21 (m, 15H), 1.40 (s, 9H), 0.99 (br, 2H)
IR: 3314, 2978, 1691, 1639, 1541, 1450, 1367, 1165, 1049

Example 111

Trans-4-[(S)-N-[(R)-N'-isopropoxycarbonyl-O-t-butyl-threonyl] prolyl] aminomethylcyclohexanecarboxamidoxime (compound No. 993 of Table 1)

NMR ($CDCl_3$)
7.24 (m, 1H), 5.43 (d, 1H), 4.85 (m, 1H), 4.57 (d, 1H), 4.47 (br, 2H), 4.23 (t, 1H), 3.92 (t, 1H), 3.80-3.70 (m, 2H), 3.06 (m, 2H), 2.36 (m, 1H), 2.00-1.20 (m, 12H), 1.23 (s, 9H) 1.23 (dd, 6H), 1.15 (d, 3H), 1.10-0.90 (m, 2H)
IR: 3354, 2978, 1699, 1649, 1543, 1448, 1373, 1257, 1192, 1111, 1032

Example 112

Trans-4-[(S)-N-[(R)-2-acetoxy-cyclohexylacetyl] prolyl] aminomethylcyclohexanecarboxamidoxime (compound No. 994 of Table 1)

NMR ($CDCl_3$)
6.80 (br, 1H), 4.61 (t, 2H), 4.49 (br, 2H), 3.90-3.84 (m, 1H), 3.51-3.40 (m, 1H), 3.10-2.85 (m, 2H), 2.38 (br, 1H), 2.11 (s, 3H), 2.06-0.80 (m, 25H)
IR: 3484, 3389, 2928, 2855, 1725, 1649, 1451, 1250

Example 113

Trans-4-[(S)-N-[(R)-N'-isopropoxycarbonyl-O-(1'-methylcyclopentyl)-seryl] prolyl]-aminomethylcyclohexanecarboxamidoxime (compound No. 995 of Table 1)

NMR ($CDCl_3$)
7.18 (m, 1H), 5.42 (m, 1H), 4.85 (m, 2H), 4.60-4.49 (m, 4H), 3.73 (m, 2H), 3.57-3.42 (m, 2H), 3.08 (m, 1H), 2.40 (m, 1H), 2.04-1.20 (m, 21H), 1.27-1.20 (m, 9H), 1.03-0.94 (m, 2H)
IR: 3356, 2932, 1695, 1653, 1541, 1448, 1263, 1111, 1030, 918

According to the same procedures as that described in Example 48, the following compounds of Examples 114 to 122 were synthesized.

Example 114

Trans-4-[(S)-N-[(R)-2-t-butyloxycarbonylamino-4,4-dimethylpentanoyl] prolyl]-aminomethylcyclohexanecarboxamide O-methoxycarbonyloxime (compound No. 533 of Table 1)

NMR ($CDCl_3$)

7.14 (br, 1H), 5.04 (d, 1H), 4.74 (br, 1H), 4.58 (d, 1H), 4.40-4.30 (m, 1H), 4.00-3.85 (m, 1H), 3.94 (s, 3H), 3.46 (q, 1H), 3.30-3.20 (m, 1H), 2.95-2.88 (m, 1H), 2.42 (br, 1H), 2.26 (t, 1H), 2.00-1.73 (m, 11H), 1.54-1.26 (m, 4H), 1.43 (s, 9H), 1.00 (s, 9H)

IR: 3347, 2955, 2870, 1765, 1645, 1539, 1443, 1254, 1169, 879

Example 115

Trans-4-[(S)-N-[(R)-N'-isopropoxycarbonyl-leucyl] prolyl] aminomethylcyclohexanecarboxamide O-methoxycarbonyloxime (compound No. 540 of Table 1)

NMR ($CDCl_3$)

7.11 (br, 1H), 5.18 (d, 1H), 4.90-4.70 (m, 1H), 4.77 (br, 2H), 4.56 (d, 1H), 4.40-4.30 (m, 1H), 3.95-3.86 (m, 1H), 3.85 (s, 3H), 3.46 (q, 1H), 3.20-2.95 (m, 2H), 2.40-2.30 (m, 1H), 2.30-2.10 (m, 1H), 2.00-1.20 (m, 13H), 1.23 (dd, 6H), 1.04-0.89 (m, 8H)

IR: 3354, 2957, 2932, 2872, 2363, 2341, 1763, 1643, 1541, 1443, 1260

Example 116

Trans-4-[(S)-N-[(R)-N'-ethoxycarbonyl-O-t-butyl-seryl] prolyl] aminomethylcyclohexanecarboxamide O-methoxycarbonyloxime (compound No. 996 of Table 1)

NMR ($CDCl_3$)

7.20 (m, 1H), 5.34 (m, 1H), 4.70 (s, 2H), 4.61 (m, 1H), 4.50 (m, 1H), 4.12-4.06 (m, 2H), 3.85 (s, 3H), 3.74 (m, 2H), 3.60-3.39 (m, 2H), 3.06 (m, 2H), 2.41-1.20 (m, 13H), 1.25 (t, 3H), 1.16 (s, 9H), 1.08-0.94 (m, 2H)

IR: 3348, 2976, 1768, 1703, 1645, 1541, 1442, 1255, 1053, 879, 752

Example 117

Trans-4-[(S)-N-[(R)-2-hydroxy-4-methyl-pentanoyl] prolyl] aminomethylcyclohexanecarboxamide O-methoxycarbonyloxime (compound No. 997 of Table 1)

NMR ($CDCl_3$)

7.07 (m, 1H), 4.73 (br, 2H), 4.52 (d, 1H), 4.23 (m, 4H), 3.56 (m, 1H), 3.40 (m, 1H), 3.13 (m, 3H), 2.41 (m, 1H), 2.30-0.90 (m, 15H), 1.33 (t, 3H), 0.97 (dd, 6H)

IR: 3346, 2932, 1759, 1641, 1450, 1369, 1251, 1078, 920, 846

Example 118

Trans-4-[(S)-N-[(R)-N'-ethoxycarbonyl-O-t-butyl-seryl] prolyl] aminomethylcyclohexanecarboxamide O-acetyloxime (compound No. 998 of Table 1)

NMR ($CDCl_3$)

7.20 (m, 1H), 5.33 (m, 1H), 4.69 (s, 2H), 4.60 (m, 1H), 4.51 (m, 1H), 4.17-4.07 (m, 2H), 3.77-3.65 (m, 2H), 3.60-3.46 (m, 2H), 3.09-3.08 (m, 2H), 2.40-1.00 (m, 13H), 2.15 (s, 3H), 1.25 (t, 3H), 1.16 (s, 9H), 1.14-0.94 (m, 2H)

IR: 3346, 2976, 1641, 1541, 1448, 1234, 1053, 754

Example 119

Trans-4-[(S)-N-[(R)-N'-isopropoxycarbonyl-O-t-butyl-seryl] prolyl] aminomethylcyclohexanecarboxamide O-methoxycarbonyloxime (compound No. 999 of Table 1)

NMR ($CDCl_3$)
7.23 (t, 1H), 5.26 (d, 1H), 4.85 (m, 1H), 4.71 (m, 1H), 4.59 (d, 1H), 4.49 (m, 1H), 3.85 (s, 3H), 3.73 (m, 2H), 3.61-3.49 (m, 2H), 3.06 (t, 2H), 2.36 (m, 1H), 2.26 (t, 3H), 2.10-1.20 (m, 11H), 1.21 (dd, 6H), 1.16 (s, 9H), 1.10-0.90 (m, 2H)
IR: 3348, 2978, 1768, 1703, 1649, 1541, 1444, 1259, 1192, 1109

Example 120

4-N-ethoxycarbonyl-amidino-[(S)-N-[(R)-2-methylsulfonylamino-4,4-dimethylpentanoyl] prolyl]-aminomethylbenzene (compound No. 1000 of Table 1)

NMR ($CDCl_3$)
7.29 (d, 2H), 7.30 (d, 2H), 7.23 (t, 1H), 5.53 (br, 1H), 4.52-4.37 (m, 2H), 4.24-4.17 (m, 2H), 4.20 (q, 2H), 3.90-3.80 (m, 1H), 3.50-3.40 (m, 1H), 2.77 (s, 3H), 2.28-2.20 (m, 4H), 1.84 (br, 2H), 1.60-1.40 (m, 2H), 1.34 (t, 3H), 1.02 (s, 9H)
IR: 3378, 2957, 2876, 2364, 2230, 1628, 1267, 1147

Example 121

4-N-methoxycarbonyl-amidino-[(S)-N-[(R)-2-methylsulfonylaminocyclohexylacetyl] prolyl]-aminomethylbenzene (compound No. 1001 of Table 1)

NMR ($CDCl_3$)
7.78 (d, 2H), 7.29 (d, 2H), 7.27 (t, 1H), 5.49 (d, 1H), 4.56 (d, 1H), 4.42 (dq, 2H), 3.77 (s, 3H), 3.80-3.70 (m, 2H), 3.60-3.51 (m, 1H), 2.79 (s, 3H), 2.28-1.60 (m, 12H), 1.20-0.95 (m, 5H)
IR: 3376, 2930, 2855, 2365, 1626, 1528, 1501, 1439, 1271, 1144

Example 122

Trans-4-N-methoxycarbonyl-amidino-[(S)-N-[(R)-2-ethoxycarbonylamino-4,4-dimethylpentanoyl] prolyl] aminomethylcyclohexane (compound No. 599 of Table 1)

NMR ($CDCl_3$)
7.08 (br, 1H), 5.17 (d, 1H), 4.56 (d, 1H), 4.50-4.40 (m, 1H), 4.20-3.80 (m, 3H), 3.70 (s, 3H), 3.47 (q, 1H), 3.20-3.00 (m, 2H), 2.45-2.30 (m, 1H), 2.20-1.30 (m, 15H), 1.24 (t, 3H), 0.99 (s, 9H), 1.10-0.89 (m, 2H)
IR: 3366, 2953, 2365, 1780, 1697, 1640, 1533, 1441, 1271, 1055

According to the same procedures as that described in Example 52, the following compounds of Examples 123 to 125 were synthesized.

Example 123

Trans-4-amino-[(S)-N-[(R)-2-carboxymethylsulfonylamino-heptanoyl]prolyl]aminomethylcyclohexane (compound No. 791 of Table 1) hydrochloride

NMR (DMSO-d^6)
7.97 (m, 2H), 7.57 (m, 1H), 4.19 (m, 2H), 4.01 (d, 1H), 3.80 (d, 1H), 3.68 (m, 1H), 3.50 (m, 1H), 2.88 (m, 3H), 2.04 (m, 1H), 1.90 (m, 5H), 1.73 (m, 4H), 1.58-1.13 (m, 12H), 1.00-0.84 (m, 5H)
IR: 3387, 2934, 1726, 1637, 1553, 1452, 1325, 1159, 1090, 1046, 604

Example 124

Trans-4-amino-[(S)-N-[(R)-N'-methylsulfonyl-O-methytyrosyl] prolyl] aminomethylcyclohexane (compound No. 1002 of Table 1) hydrochloride

NMR (DMSO-d^6)
8.10 (br, 3H), 7.77 (t, 1H), 7.67 (d, 1H), 7.17 (d, 2H), 6.87 (d, 2H), 4.25-4.16 (m, 1H), 3.75 (br, 2H), 3.73 (s, 3H), 3.57-3.40 (m, 1H), 3.00-2.70 (m, 5H), 2.77 (s, 3H), 2.00-1.71 (m, 8H), 1.40-1.20 (m, 3H), 1.00-0.80 (m, 2H)
IR: 3385, 2936, 2363, 1639, 1514, 1450, 1304, 1248, 1149

Example 125

Trans-4-amino-[(S)-N-[(R)-N'-ethoxycarbonyl-O-t-butyloxy-seryl] prolyl] aminomethylcyclohexane (compound No. 1003 of Table 1) hydrochloride

NMR (DMSO-d^6)
8.29 (s, 3H), 7.20 (s, 1H), 5.69 (d, 1H), 4.58-4.47 (m, 2H), 4.12 (m, 2H), 3.82 (m, 1H), 3.61-3.48 (m, 2H), 3.09 (m, 2H), 2.32-0.86 (m, 15H), 1.27 (t, 3H), 1.16 (s, 9H)
IR: 3358, 2974, 1645, 1541, 1448, 1257, 1192, 1053

According to the same procedures as that described in Example 67, the following compounds 126 to 130 were synthesized.

Example 126

Trans-4-(5-methyl-1,3-dioxo-2-on-4-ylmethyl)amino-[(S)-N-[(R)-2-hydroxy-cyclohexylacetyl] prolyl]-aminomethylcyclohexane (compound No. 966 of Table 1)

NMR ($CDCl_3$)
7.08 (m, 1H), 4.54 (d, 1H), 4.06 (m, 1H), 3.59 (m, 1H), 3.49 (s, 2H), 3.46 (m, 1H), 3.07 (m, 2H), 2.48 (m, 2H), 2.11 (s, 3H), 2.01 (m, 2H), 1.90-1.70 (m, 10H), 1.58 (m, 3H), 1.41-0.94 (m, 10H)
IR: 3387, 2928, 2855, 1821, 1736, 1638, 1543, 1451, 1387, 1223, 1107, 999, 712

Example 127

Trans-4-(5-methyl-1,3-dioxo-2-on-4-ylmethyl)amino-[(S)-N-[(R)-N'-methylsulfonyl-phenylalanyl] prolyl]-aminomethylcyclohexane (compound No. 967 of Table 1)

NMR ($CDCl_3$)
7.35-7.20 (m, 5H), 6.71 (t, 1H), 5.48 (d, 1H), 4.44 (m, 1H), 4.25 (m, 1H), 3.60 (m, 1H), 3.48 (s, 2H), 3.09 (m, 1H), 2.96 (m, 3H), 2.78 (s, 3H), 2.77 (m, 1H), 2.50 (m, 1H), 2.20 (m, 1H), 2.11 (s, 3H), 1.88-1.56 (m, 8H), 1.42 (m, 1H), 1.24 (m, 2H), 0.96 (m, 2H)
IR: 3387, 2930, 1819, 1736, 1649, 1541, 1499, 1451, 1318, 1223, 1152, 999

Example 128

Trans-4-(5-methyl-1,3-dioxo-2-on-4-ylmethyl)amino-[(S)-N-[(R)-2-ethoxycarbonylamino-cyclohexylacetyl] prolyl]aminomethylcyclohexane (compound No. 1004 of Table 1)

NMR ($CDCl_3$)
7.11 (m, 1H), 5.31 (m, 1H), 4.58 (d, 1H), 4.10 (t, 2H), 4.04 (m, 1H), 3.94 (m, 1H), 3.56 (m, 1H), 3.49 (s, 2H), 3.04 (m, 2H), 2.52 (m, 1H), 2.36 (m, 2H), 2.12 (s, 3H), 2.00 (m, 3H), 1.92-1.62 (m, 10H), 1.43 (m, 2H), 1.25 (q, 3H), 1.22 (m, 4H), 1.06 (m, 4H)
IR: 3353, 2930, 2855, 1823, 1653, 1537, 1449, 1223, 1040, 999, 772, 627

Example 129

Trans-4-(5-methyl-1,3-dioxo-2-on-4-ylmethyl)amino-[(S)-N-[(R)-2-isopropoxyamino-4,4-dimethyl-pentanoyl] prolyl]aminomethylcyclohexane (compound No. 1005 of Table 1)

NMR ($CDCl_3$)

7.10 (m, 1H), 5.07 (d, 1H), 4.83 (m, 1H), 4.57 (d, 1H), 4.40 (m, 1H), 3.96 (m, 1H),3.48 (s, 2H), 3.45 (m, 2H), 3.04 (m, 2H), 2.50 (m, 1H), 2.39 (m, 1H), 2.11 (s, 3H), 2.00 (m, 3H), 1.83 (m, 3H), 1.69 (m, 5H), 1.57-1.42 (m, 3H), 1.25 (d, 3H), 1.22 (d, 3H), 1.00 (s, 9H)

IR: 3349, 2934, 2872, 1823, 1653, 1537, 1445, 1225, 1047, 999, 712, 627

Example 130

Trans-4-(5-methyl-1,3-dioxo-2-on-4-ylmethyl)amino-[(S)-N-[(R)-2-methylsulfonylamino-cyclohexylacetyl] prolyl]aminomethylcyclohexane (compound No. 1006 of Table 1)

NMR ($CDCl_3$)

6.69 (t, 1H), 5.26 (d, 1H), 3.82 (m, 2H), 3.54 (m, 2H), 3.49 (s, 2H), 3.13 (m, 1H), 3.00 (m, 1H), 2.96 (s, 3H), 2.51 (m, 1H), 2.30 (m, 1H), 2.11 (s, 3H), 2.02 (m, 4H), 1.80 (m, 9H), 1.61 (m, 2H), 1.43 (m, 1H), 1.20 (m, 5H), 0.97 (m, 3H)

IR: 3376, 2930, 2855, 1642, 1536, 1451, 1352, 1154, 984, 760, 619, 517

Experimental Example 1: Determination of antithrombin activity

(i) The measuring method for hydrolysis inhibition of synthetic substrate (S-2238)

S-2238 (manufactured by Kabi Co.) is dissolved in a Tris hydrochloric acid buffer solution (pH: 8.3) to prepare a S-2238-0.4 M Tris hydrochloric acid solution having a concentration of 80 μm. To 175 μl of the solution, an aqueous solution of a compound of the present invention (515 μl) is added. After incubating at 37 °C for one minute, 10 μl of a bovine thrombin solution (4.4 units/ml, manufactured by Mochida Co., Ltd.) is added. A hydrolysis reaction rate of the substrate is determined by measuring a change in absorbance of 405 nm at 37 °C.

The inhibitor concentration exhibiting an absorbance which is half as large as that obtained in case of adding no inhibitor (compound of the present invention) was determined as I_{50} (μm).

(ii) The measuring method for coagulation inhibition of rat plasma

The compound of the present invention is dissolved in water or saline to form a solution of a total volume of 0.1 ml. To the solution, 0.1 ml of rat plasma is added and the mixture is incubated at 37 °C for 30 seconds. Then, 0.1 ml of bovine thrombin (8 units/ml, Mochida Co., Ltd.) is added and the coagulation time is measured at 37 °C. The concentration of the inhibitor (i.e., the compound of the present invention) which doubles the coagulation time that obtained in the absence of the inhibitor was determined as I_{50} (μm).

(iii) The measuring method for antithrombin activity of rat plasma on oral administration

To a rat abstained from bait overnight, an aqueous solution or suspension of the present compound (inhibitor) (30 mg/kg) is orally administered using an oral sound.

After one hour, 2 ml of blood is collected from cava abdominalis and the antithrombin activity in plasma is measured using a method of the above item (ii). As a control experiment, the coagulation time of blood collected from a rat which has not been administered the inhibitor was measured. The extension effect on the coagulation time is represented by the numerical value obtained by comparing the data with those obtained in control experiment, wherein the numerical value obtained in the control experiment was assumed to be 1.

Experimental Example 2: Determination of Antitrypsin activity

(i) The measuring method for hydrolysis inhibition of synthetic substrate (S-2222)

S-2222 (manufactured by Kabi Co.) is dissolved in a Tris hydrochloric acid (pH: 8.3) to prepare a S-2222-0.4M Tris hydrochloric acid solution having a concentration of 400 μm. To the solution (175 μl), 515 μl of a solution of a compound of the present invention is added. After incubating at 37 °C for one minute, 10 μl of a bovine trypsin solution (1 to 2 mg/ml, manufactured by Sigma Co.) is added. A hydrolysis reaction rate of the substrate is determined by measuring a change in absorbance of 405 nm at 37 °C.

The inhibitor concentration exhibiting an absorbance which is half as large as that obtained in case of adding no inhibitor (compound of the present invention) was determined as I_{50} (μm).

The results are shown in Table 2.

Table 2

Example No.	Antithrombin activity I_{50} (μm) Synthetic substrate method	Rat plasma method	Antitrypsin activity I_{50} (μm)	Thrombin coagulation time extension coefficient on oral administration
1		0.046		5.97
2		0.030		8.75
3		0.027		4.46
4	0.0076	0.021	0.040	6.70
5		0.048		
6		0.056		3.16
7		0.030		
8		0.122		
9		0.11		
10		0.17		
12		0.083		
13	0.72	0.59		
15	0.011	0.038	2.2	
16	0.021		1.7	
17	0.015	0.053	3.2	
18		0.060		
19		0.031		
20		0.028		
21	0.021		1.0	
22	0.014		0.94	
23	0.017	0.058	3.6	
24				3.28
25		> 300		2.82
26				4.16
27				3.52
28				4.35
30				2.75
31				2.77
32				3.58

Example No.	Antithrombin activity I_{50} (μm) Synthetic substrate method	Rat plasma method	Antitrypsin activity I_{50} (μm)	Thrombin coagulation time extension coefficient on oral administration
33				3.99
35				3.72
36				2.85
37				4.37
39				2.37
40				2.70
41				2.94
42				4.36
43				3.09
46				2.16
47				2.34
48				4.91
49				7.12
50				3.50
51				2.80
52	0.13	0.045	14	4.10
53	0.081	0.059	1.4	
54		0.23		
56	0.13	0.080	14	2.10
57		0.082		
58		0.097		2.35
61		0.056		
62		0.088		2.18
64		0.13		1.25
65				3.67
67	0.56	0.081	20	

Experimental Example 3: Acute toxicity test

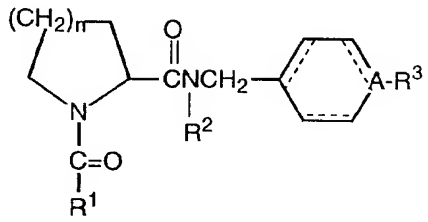
Acute toxicity was determined in rat. An approximate lethal dose was determined by conducting an oral acute toxicity test using rats. The results are shown in Table 3.

Table 3

Example No.	Approximate lethal dose mg/kg	
	Male	Female
4	750	1500
52	Not less than 2000	Not less than 2000
33	Not less than 2000	Not less than 2000
37	Not less than 2000	Not less than 2000

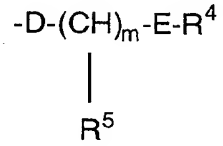
Claims

1. A prolineamide derivative represented by the formula (I):



(I)

wherein A is a carbon atom or a nitrogen atom;
n is an integer of 0 to 2;
a broken line is no bond or a single bond;
R^1 is



{wherein D and E independently indicate a single bond or an optionally branched C_1-C_6 alkylene group;

R^4 is a C_1-C_6 alkyl group; -OR^6 (R^6 is a hydrogen atom, a C_1-C_6 alkyl group, an optionally substituted C_6-C_{10} aryl group, an optionally substituted C_3-C_8 cycloalkyl group or an optionally substituted C_7-C_{12} aralkyl group), -SR^7 (R^7 is a C_1-C_6 alkyl group, an optionally substituted C_6-C_{10} aryl group, an optionally substituted C_3-C_8 cycloalkyl group or an optionally substituted C_7-C_{12} aralkyl group), -SOR^8 (R^8 is an optionally substituted C_6-C_{10} aryl group or an optionally substituted C_3-C_8 cycloalkyl group), -SO_2R^9 (R^9 is an optionally substituted C_6-C_{10} aryl group or an optionally substituted C_3-C_8 cycloalkyl group), -COR^{10} (R^{10} is a hydroxyl group, a C_1-C_6 alkoxy group, an optionally substituted C_6-C_{10} aryl group or an optionally substituted C_3-C_8 cycloalkyl group), -NHR^{11} (R^{11} is a C_1-C_6 alkyl group, an optionally substituted C_6-C_{10} aryl group, an optionally substituted C_3-C_8 cycloalkyl group or an optionally substituted C_7-C_{12} aralkyl group), -$NHCOR^{12}$ (R^{12} is a C_1-C_6 alkoxy group, an optionally substituted C_6-C_{10} aryl group, an optionally substituted C_3-C_8 cycloalkyl group or an optionally substituted C_7-C_{12} aralkyloxy group), -$NHSO_2R^{13}$ (R^{13} is a C_1-C_6 alkyl group, an optionally substituted C_6-C_{10} aryl group, an optionally substituted C_3-C_8 cycloalkyl group, an optionally substituted C_7-C_{12} aralkyl group, or an optionally substituted 5- to 10-membered heterocyclic group), an optionally substituted C_6-C_{10} aryl group, an optionally substituted C_3-C_8 cycloalkyl group, an optinally substituted 5- to 10-membered heterocyclic group or -$SiR^{14}R^{15}R^{16}$ (R^{14}, R^{15}, and R^{16} independently indicate a C_1-C_6 alkyl group);

R^5 is a -OR^{17} (R^{17} is a hydrogen atom, -$SiR^{22}R^{23}R^{24}$ (R^{22}, R^{23}, and R^{24} independently indicate a C_1-C_6 alkyl group), a C_1-C_6 alkyl group, or an optionally substituted 5- to 10-membered heterocyclic group)), -$OCOR^{18}$ (R^{18} is a hydrogen atom, a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, an amino group, a C_1-C_6 alkylamino group, a C_2-C_{12} dialkylamino group or a C_2-C_7 alkenylamino group), -NHR^{19} (R^{19} is a hydrogen atom, a C_1-C_6 alkyl group or an optionally substituted C_7-C_{12} aralkyl group), $NHCOR^{20}$ (R^{20} is a hydrogen atom, a C_1-C_5 alkyl group, a C_1-C_6 haloalkyl group, a C_1-C_6 alkoxy group, an optionally substituted C_3-C_8 cycloalkyl group, a C_2-C_7 carboxyalkyloxy group, a C_2-C_7 alkenyloxy group, an optionally substituted C_6-C_{10} aryl group, an optionally substituted C_6-C_{10} aryloxy group, a C_3-C_9 alkoxycarbonylalkoxy group, a C_2-C_{12} dialkylamino group or an optionally substituted C_7-C_{12} aralkyloxy group) or -$NHSO_2R^{21}$ (R^{21} is a C_1-C_6 alkyl group, a C_1-C_6 haloalkyl group, a C_2-C_7 carboxyalkyl group, an optionally substituted C_6-C_{10} aryl group, a C_3-C_9 alkoxycarbonylalkyl group or an optionally

substituted C_7-C_{12} aralkyl group); and m is 0 or 1};

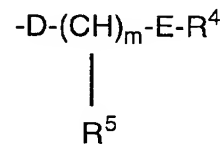
R^2 is a hydrogen atom or a C_1-C_6 alkyl group; and R^3 is -C(=NR^{25})NH_2 (R^{25} is a hydrogen atom, a C_1-C_6 alkyl group, a C_2-C_7 acyl group, a C_2-C_7 acyloxy group, a C_1-C_6 alkoxy group, a C_2-C_7 alkoxycarbonyl group, a C_2-C_7 alkoxycarbonyloxy group, a hydroxyl group or a C_2-C_7 hydroxyalkylcarbonyloxy group), -NH-C(=NR^{25})NH_2 (R^{25} is as defined above) or -NHR^{26} (R^{26} is a hydrogen atom, a C_1-C_6 alkyl group, a C_2-C_7 acyl group, a C_2-C_7 alkoxycarbonyl group or a 5-C_1-C_3 alkyl-1,3-dioxol-2-on-4-ylmethyl group); provided that R^3 is -C(=NR^{25})NH_2 (R^{25} is as defined above) when A is a nitrogen atom , or a salt or hydrate thereof.

2. The compound according to claim 1, wherein the 5- to 10-membered heterocyclic group contains 1 to 4 heteroatoms selected from the group consisting of an oxygen atom, a sulfur atom and a nitrogen atom and the total number of atoms constituting the ring is 5 to 10.

3. The compound according to claim 1 or 2, wherein the substituent is a group selected from the goup consisting of a C_1-C_6 alkyl group, a C_1-C_6 haloalkyl group, a C_1-C_6 alkoxy group, a hydroxyl group, a carboxyl group, a C_2-C_7 carboxyalkyl group, a C_2-C_7 carboxyalkyloxy group, a C_2-C_7 acyl group, a C_2-C_7 acyloxy group, a C_2-C_7 alkoxycarbonyl group, a C_2-C_7 alkoxycarbonyloxy group, a C_8-C_{13} aralkyloxycarbonyl group, a C_3-C_9 alkoxycarboxyalkoxy group and a halogen atom.

4. The compound according to any one of claims 1 to 3, wherein A is a carbon atom.

5. The compound according to claim 1 or 4, wherein n is 1 or 2; R^1 is



{wherein D and E independently indicate a single bond or an optionally branched C_1-C_6 alkylene group;

R^4 is a C_1-C_6 alkyl group; -OR^6 (R^6 is a C_1-C_6 alkyl group; a C_6-C_{10} aryl group which may be substituted with at least one substituent selected from the group consisting of a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a halogen atom, a hydroxyl group, a carboxyl group, a C_2-C_7 alkoxycarbonyl group, a C_2-C_7 carboxyalkyl group, a C_2-C_7 acyl group, a C_2-C_7 acyloxy group, a C_2-C_7 alkoxycarbonyloxy group, a C_3-C_9 alkoxycarbonylalkoxy group and a benzyloxycarbonyl group; or a C_7-C_{12} aralkyl group which may be substituted with at least one substituent selected from the group consisting of a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a halogen atom, a hydroxyl group, a carboxyl group, a C_2-C_7 alkoxycarbonyl group, a C_2-C_7 carboxyalkyl group, a C_2-C_7 acyl group, a C_2-C_7 acyloxy group, a C_2-C_7 alkoxycarbonyloxy group, a C_3-C_9 alkoxycarbonylalkoxy group and a benzyloxycarbonyl group); -SR^7 (R^7 is a C_1-C_6 alkyl group; a C_6-C_{10} aryl group which may be substituted with at least one substituent selected from the group consisting of a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a halogen atom, a hydroxyl group, a carboxyl group, a C_2-C_7 alkoxycarbonyl group, a C_2-C_7 carboxyalkyl group, a C_2-C_7 acyl group, a C_2-C_7 acyloxy group, a C_2-C_7 alkoxycarbonyloxy group, a C_3-C_9 alkoxycarbonylalkoxy group and a benzyloxycarbonyl group; or a C_7-C_{12} aralkyl group which may be substituted with at least one substituent selected from the group consisting of a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a halogen atom, a hydroxyl group, a carboxyl group, a C_2-C_7 alkoxycarbonyl group, a C_2-C_7 carboxyalkyl group, a C_2-C_7 acyl group, a C_2-C_7 acyloxy group, a C_2-C_7 alkoxycarbonyloxy group, a C_3-C_9 alkoxycarbonylalkoxy group and a benzyloxycarbonyl group); -COOH; a C_6-C_{10} aryl group which may be substituted with at least one substituent selected from the group consisting of a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a halogen atom, a hydroxyl group, a carboxyl group, a C_2-C_7 alkoxycarbonyl group, a C_2-C_7 carboxyalkyl group, a C_2-C_7 acyl group, a C_2-C_7 acyloxy group, a C_2-C_7 alkoxycarbonyloxy group, a C_3-C_9 alkoxycarbonylalkoxy group and a benzyloxycarbonyl group; a C_3-C_8 cycloalkyl group; or -$SiR^{14}R^{15}R^{15}$ (R^{14}, R^{15}, and R^{15} independently indicate a C_1-C_6 alkyl group);

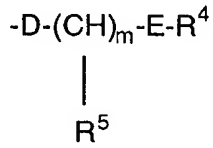
R^5 is -OH, -$OCOR^{18}$ (R^{18} is a C_1-C_6 alkoxy group or a C_2-C_7 alkenylamino group), -NH_2,

$-NHCOR^{20}$ (R^{20} is a C_1-C_6 alkoxy group, a C_6-C_{10} aryloxy group, a C_3-C_9 alkoxycarbonylalkoxy group, a C_2-C_{12} dialkylamino group or a C_7-C_{12} aralkyloxy group) or $-NHSO_2R^{21}$ (R^{21} is a C_1-C_6 alkyl group, a C_2-C_7 carboxyalkyl group, a C_6-C_{10} aryl group, a C_3-C_9 alkoxycarbonylalkyl group or a C_7-C_{12} aralkyl group); and m is 0 or 1};

R^2 is a hydrogen atom; and

R^3 is $-C(=NR^{25})NH_2$ (R^{25} is a hydrogen atom, a C_2-C_7 alkoxycarbonyl group or a hydroxyl group), $-NH-C(=NR^{25})NH_2$ (R^{25} is as defined above) or $-NHR^{26}$ (R^{26} is a hydrogen atom, a C_2-C_7 alkoxycarbonyl group or a 5-C_1-C_3 alkyl-1,3-dioxol-2-on-4-ylmethyl group).

6. The compound according to claim 1 or 4, wherein n is 1; R^1 is



{wherein D and E independently indicate a single bond or an optionally branched C_1-C_6 alkylene group;

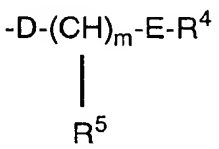
R^4 is a C_1-C_6 alkyl group; $-OR^6$ (R^6 is a C_6-C_{10} aryl group which may be substituted with at least one substituent selected from the group consisting of a C_1-C_6 alkyl group, a halogen atom, a carboxyl group, a C_2-C_7 carboxyalkyl group and a benzyloxycarbonyl group or C_7-C_{12} aralkyl group); $-SR^7$ (R^7 is a C_1-C_6 alkyl group); a C_6-C_{10} aryl group which may be substituted with at least one substituent selected from the group consisting of a C_1-C_6 alkyl group, a halogen atom, a carboxyl group, a C_2-C_7 carboxyalkyl group and a benzyloxycarbonyl group; or a C_3-C_6 cycloalkyl group;

R^5 is $-OH$, NH_2, $-NHCOR^{20}$ (R^{20} is a C_1-C_6 alkoxy group or a C_7-C_{12} aralkyloxy group) or $-NHSO_2R^{21}$ (R^{21} is a C_1-C_6 alkyl group or a C_6-C_{10} aryl group); and m is 1};

R^2 is a hydrogen atom; and

R^3 is $-C(=NR^{25})NH_2$ (R^{25} is a hydrogen atom or a hydroxyl group) or $-NH_2$.

7. The compound according to claim 1 or 4, wherein n is 1; R^1 is



{wherein D is a single bond; E is a single bond or a C_1-C_6 alkylene group;

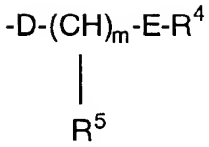
R^4 is a C_1-C_6 alkyl group; $-OR^6$ (R^6 is a C_6-C_{10} aryl group which may be substituted with at least one substituent selected from the group consisting of a C_1-C_6 alkyl group, a halogen atom, a carboxyl group, a C_2-C_7 carboxyalkyl group and a benzyloxycarbonyl group or C_7-C_{12} aralkyl group); $-SR^7$ (R^7 is a C_1-C_6 alkyl group); a C_6-C_{10} aryl group which may be substituted with at least one or more substituents selected from the group consisting of a C_1-C_6 alkyl group, a halogen atom, a carboxyl group, a C_2-C_7 carboxyalkyl group and a benzyloxycarbonyl group; or a C_3-C_6 cycloalkyl group;

R^5 is $-NH_2$, $-NHCOR^{20}$ (R^{20} is a C_1-C_6 alkoxy group or a C_7-C_{12} aralkyloxy group) or $-NHSO_2R^{21}$ (R^{21} is a C_1-C_6 alkyl group or a C_6-C_{10} aryl group); and m is 1};

R^2 is a hydrogen atom; and

R^3 is-$C(=NR^{25})NH_2$ (R^{25} is a hydrogen atom or a hydroxyl group) or $-NH_2$.

8. The compound according to claim 1,wherein A is a carbon atom; n is 1; R^1 is

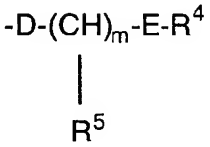


{wherein D is a single bond; E is a single bond or a C_1-C_3 alkylene group; R^4 is a C_3-C_6 alkyl group, $-OR^6$ (R^6 is a C_1-C_6 alkyl group, a phenyl group, or a C_3-C_6 cycloalkyl group; R^5 is-OH,$-NHR^{19}$ (R^{19} is a hydrogen atom), $-NHCOR^{20}$ (R^{20} is a C_1-C_6 alkoxy group) or $-NHSO_2R^{21}$ (R^{21} is a C_1-C_3 alkyl group); and m is 1};

R^2 is a hydrogen atom; and

R^3 is $-C(=NR^{25})NH_2$ (R^{25} is a hydrogen atom or a hydroxyl group) or $-NH_2$.

9. The compound according to claim 1 or 4, wherein n is 1; R^1 is



{D is a single bond; E is a single bond or a C_1-C_6 alkylene group; R^4 is a C_1-C_6 alkyl group; R^5 is $-NHCOR^{20}$ (R^{20} is a C_1-C_6 alkoxy group); and m is 1};

R^2 is a hydrogen atom; and

R^3 is $-C(=NR^{25})NH_2$ (R^{25} is a hydrogen atom or a hydroxyl group).

10. Trans-4-[(S)-N-((R)-2-ethoxycarbonylamino-4,4-dimethylpentanoyl) prolyl]aminomethylcyclohexane-carboxamidoxime or a salt or hydrate thereof.

11. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 10 and a pharmaceutically acceptable carrier therefor.

12. The use of a compound as claimed in any one of claims 1 to 10 in the manufacture of a medicament effective as a protease inhibitor.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 95 10 1059

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X	CHEMICAL ABSTRACTS, vol. 104, no. 7, 17 February 1986, Columbus, Ohio, US; abstract no. 47665b, * abstract * & SYMP. BIOL. HUNG. (PROTEINASE ACTION), vol.25, 1984, BUDAPEST pages 277 - 298 S. BAJUSZ & CAS REGISTRY HANDBOOK 1986 SUPPL. (STN DATABASE) * RN: 99742-41-3 *	1	C07D207/16 C07D211/60 C07D403/06 C07D403/12 C07D401/12 C07D403/08 C07D403/10 C07K5/06 A61K31/40
X,P	EP-A-0 601 459 (BRISTOL-MYERS SQUIBB CO.) * see ex. 30,32-35,47,49-53 *	1	
A	CHEMICAL ABSTRACTS, vol. 103, no. 3, 22 July 1985, Columbus, Ohio, US; abstract no. 18900y, * abstract * & BIOCHEMISTRY, vol.24, no.13, 1985, EASTON, PA US pages 3149 - 3157 C.F. VENCILL ET AL.	1	
A	CHEMICAL ABSTRACTS, vol. 92, no. 3, 21 January 1980, Columbus, Ohio, US; abstract no. 17850z, * abstract * & BIOORG. CHEM., vol.8, no.3, 1979 pages 299 - 309 C.H. HASSALL ET AL.	1	
A	WO-A-93 15756 (CORVAS INTERNATIONAL, INC.) * the whole document *	1	

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TECHNICAL FIELDS SEARCHED (Int.Cl.6)

C07D
C07K
A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
BERLIN	14 June 1995	Frelon, D

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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A : technological background
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D : document cited in the application
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EUROPEAN SEARCH REPORT

Application Number
EP 95 10 1059

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
A D	US-A-5 153 176 (ABE ET AL.) * the whole document * & JP-A-4 089 498 (NITTO BISEKI CO., LTD.)	1	
			TECHNICAL FIELDS SEARCHED (Int.Cl.6)

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
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